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**EFFECTS OF IONIZING RADIATION AND
OF DYNAMIC FACTORS ON THE FUNCTIONS
OF THE CENTRAL NERVOUS SYSTEM -
PROBLEMS OF SPACE PHYSIOLOGY**

N. N. Livshits, Editor-in-Chief

Science Publishing House, Moscow, 1964



NATIONAL AERONAUTICS AND SPACE ADMINISTRATION • WASHINGTON, D. C. • AUGUST 1965



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ON THE FUNCTIONS OF THE CENTRAL NERVOUS SYSTEM
- PROBLEMS OF SPACE PHYSIOLOGY

N. N. Livshits, Editor-in-Chief

Translation of "Vliyaniye ioniziruyushchikh izlucheniye i dinamicheskikh
faktorov na funktsii tsentral'noy nervnoy sistemy;
voprosy kosmicheskoy fiziologii."
Izdatel'stvo Nauka, Moscow, 1964.

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

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FOREWORD

Man is frequently exposed to ionizing radiation combined with other factors during the operation of modern machines. As a result the radiation effects may change considerably. This is a matter of both practical and theoretical interest, since to understand radiation reactions we must know how they change under the influence of additional agents. Quite a few studies have dealt with the combined effects of radiation and nonradiation factors on animals, and the subject is now an independent branch of radiobiology and medicine. However, there have only been a few articles reporting on the biological effects of ionizing radiation combined with such dynamic factors as acceleration and vibration.

Our objective was to investigate the nature of the effects of radiation, acceleration and vibration on certain physiological functions. It was necessary to begin by studying the effect of each factor separately, then to determine the possibilities of the organism adapting to them and finally to ascertain how radiation changes them and how under their influence the radiation effects are themselves changed.

The first articles in this collection examine the effect of acceleration, with the following criteria serving as indices: rate of blood flow in the venous system of the brain, unconditioned motor reflexes and excitability of the vestibular apparatus. V. Ya. Klimovitskiy investigated the reactions of the cerebral venous system and the adaptive capabilities of the mature organism. The work of A. A. Gyurdzhian and coworkers, carried out under the direction of O. G. Gazenko, Doctor of Biological Sciences, deals with the reaction of animals to prolonged exposure to this factor during postnatal development, beginning with the earliest stages.

The remaining articles discuss the combined effect of ionizing radiation and vibration. The authors used lethal doses of radiation, which have a pronounced effect on the functions under study, and which permit us to determine the main patterns of the reactions to radiation and to combined agents, even in cases where large-scale experiments cannot be performed owing to the laboriousness of the methods. The main purpose of the investigators (the radiation physiology group, Institute of Biophysics, USSR Academy of Sciences, N. N. Livshits, Director) was to study the effect of these factors on some of the central nervous system functions. Part of the material contained in the works of Z. I. Apanasenko and M. A. Kuznetsova was published in abridged form in the collection "Problemy kosmicheskoy biologii" (Problems of Space Biology) Vol. 3, 1964. However, the experimental data had not yet been processed and all the conclusions could not be drawn. Some of the material from this collection has been unavoidably duplicated in this book, for otherwise the articles could not be fully understood.

A contributor to this collection is Yu. S. Demin of the Laboratory of Radiation Genetics, Institute of Biophysics, who reports a detailed investigation of the effect of radiation and vibration on bone marrow cells, which he carried out under the direction of M. A. Arsen'yeva. A comparison of the influence of these factors on different functional systems will throw light on the basic patterns.

To elucidate the mechanisms of the observed changes, it was necessary critically to review the literature dealing with the effect of vibration on the nervous system. This was done by L. D. Luk'yanova.

The combined effects of ionizing radiation and dynamic factors should be regarded as part of the general problem of the combined effects of ionizing radiation and other factors on the animal organism.

A comparison of our experimental material with the published data is found in N. N. Livshits' article.

COMBINED EFFECTS OF IONIZING RADIATION AND OTHER FACTORS

N. N. Livshits

ABSTRACT

The literature on combined effects of ionizing radiation and nonradiation factors on mammalian organisms is reviewed. The problem of the mechanism of organism response to combined factors is discussed. Published results of experimental investigations of combined effect of vibration and ionizing radiation on some animal organism functions are discussed. These studies are compared with literary data, and the mechanism of higher animal reactions to combined effect of vibration and ionizing radiations is considered. A suggestion is expressed that in responses to vibration and irradiation effects side by side with the mechanisms described in literature, parabiologic processes in the nervous system may be of great importance.

There is now an extensive literature on the general problem of the combined effects of ionizing radiation and nonradiation factors on the organism, an exhaustive review of which does not come within the scope of this article. We wish merely to discuss the current status of the problem and to compare the results of our work with the published data. /5*

Many studies dealt with the effect of combined lesions produced by ionizing radiation and other injurious agents.

N. N. Aleksandrov et al. (1962) investigated whole-body X-irradiation with a dose of 600 r and cranial trauma in rabbits. A sterile skull wound in the frontoparietal region was inflicted immediately after irradiation, using surgical instruments without anesthesia. The wound was infected with standard cultures of pathogenic microorganisms. It was treated surgically three days later. Thus, these experiments involved a combination of pain, trauma and infection. Both the penetrating and the nonpenetrating skull wounds severely complicated the course of the radiation sickness.

S. S. Sokolov (1956) inflicted on guinea pigs a skin and partial muscle wound 2.5x3.0 cm in size immediately after whole-body X-irradiation with a dose of 400 r. Some of the animals were kept without bandages in nonsterile

*Numbers given in the margin indicate the pagination in the original foreign text.

conditions, while others received sterile bandages. The wounds of the irradiated guinea pigs, even those without sterile bandages, took 3-5 days longer to heal than did the wounds of the animals traumatized without irradiation. Moreover, the trauma considerably aggravated the course of the radiation sickness. The loss of weight of the irradiated and traumatized animals was sharper and the restoration of normal weight took longer than in the irradiated, but not traumatized animals. The clinical symptoms of radiation sickness were more pronounced and mortality was higher in the first group.

Resection of the radius performed 30 min after whole-body irradiation with a dose of 600 r increased the mortality rate of rabbits and magnified the weight loss during radiation sickness (Blinov, 1958). /6

Fracture of the tubular bones in rabbits after irradiation with a dose of 900 r greatly complicated the clinical course of radiation sickness. The loss of weight was more pronounced, ulcerative-necrotic processes intensified in the tissues and mortality was higher than in the animals exposed only to irradiation (Shcherbina, 1962).

Mortality was higher among rabbits subjected to traumatic shock 30 min after whole-body irradiation with a dose of 700 r than after irradiation alone (Il'inskaya and Astakhova, 1959).

S. I. Fayn (1963) presents the results of a histological investigation of ganglia of the celiac plexus and intramural apparatus of the small intestine in rabbits receiving a wound or resection of the small intestine 24 hours after whole-body irradiation with a dose of 400 r. In animals subjected to trauma without irradiation, reactive changes in the ganglia were noted in only a few cases. Various morphological changes were observed in the celiac plexus and nerve ganglia of the small intestine in almost all irradiated rabbits.

Ye. N. Tsverava et al. (1959) exposed dogs to a shock wave produced by exploding 600-800 g of ammonal 50-60 cm away from the animal just before whole-body X-irradiation with a dose of 600-800 r. The clinical course of the ensuing radiation sickness was more severe than after irradiation alone. The individual action of each of the factors resulted in reduction of blood protein, due to decreased albumin content despite slight increase in globulin content. These phenomena were particularly marked in the dogs subjected to the combined action.

Sh. R. Topuriya et al. (1959) describes the summation of pathomorphological changes in dogs exposed to a shock wave and X-irradiation with doses calculated to cause acute radiation sickness. These animals developed hemorrhages as well as the lung changes characteristically produced by a shock wave.

G. Ye. Kevleshvili et al. (1959) found that in dogs exposed to the combined effects of a shock wave and X-irradiation (doses not mentioned) the volume of circulating blood decreased as early as the second day, i.e., sooner /7 than after irradiation without additional agents. The authors ascribe this phenomenon to the fact that in the first group of animals extensive hemorrhages developed in the viscera. This was confirmed at autopsy.

V. M. Vargunina (1962) noted that radiation sickness followed a more severe course in dogs burned with boiling water poured over 4 percent of the body surface following whole-body X-irradiation with a dose of 300 r.

D. A. Golubentsev and N. A. Shevyreva (1960) produced second- and third-degree burns over 15-17 percent of the body surface of dogs within 30 min of whole-body gamma-irradiation with doses of 100, 200, and 400 r.

These burns as well as the combination of burns and irradiation caused shock. According to the literature, burns produce persistent hyperglycemia. However, as Golubentsev and Shevyreva observed, the combination of burns and irradiation caused hypoglycemia within the first hour or two. The authors regarded this as evidence of early insufficiency of liver carbohydrate function, i.e., one of the more severe aftereffects of trauma.

B. M. Khromov (1950) concluded from a review of the literature and his own experiments that radiation lesions generally aggravate the course of mechanical and thermal traumas, which, in turn, aggravate the course and outcome of the radiation lesions. Khromov noted, however, that in very rare cases one injury may favorably affect the other.

To understand the mechanism of combined action, we must take into account the possibility of a lack of mutual aggravation or alleviation of injuries. It has been found that mutual aggravation frequently occurs only when both injurious agents achieve a certain intensity.

N. S. Dzhevadyan et al. (1958) found that traumatic shock caused by severe traumatization of muscles in the hind legs of dogs 12-20 min after whole-body irradiation with a dose of 300 r did not aggravate the course of radiation sickness in the animals. But this factor did considerably aggravate the results of irradiation with a dose of 600 r.

Clemenson and Nelson (1955) exposed groups of mice to whole-body X-irradiation with doses of 25, 50, 100, 200, 300, 400, 500 and 600 r and, a few hours later, to a shock wave which caused mild, heavy and severe lung damage. The weight and survival time of the animals were taken into account.

Among the mice subjected to the blast alone, slight mortality occurred only the first two days thereafter. The irradiated animals began to die 8-12 days later, depending on the dose. After combined action mortality began within 18 48 hours, just as it did after the blast alone, but this did not affect the 30 day survival rate of the animals.

A significant intensification of the effects of combined factors occurred only when irradiation of the highest dose used was combined with a blast of maximum power. Some groups of mice subjected to smaller doses of irradiation and to a blast of maximum power regained their normal weight sooner than did the animals exposed only to irradiation.

By way of contrast, some authors note that additional agents alter the effect of irradiation only when small doses of ionizing radiation are used

(Bychkovskaya, 1955; Zakharzhevskiy, 1960; Shcherban', 1960; others). These investigations will be discussed below.

Also of significance is the interval of time between irradiation and traumatization. I. N. Kruk (1960) describes the results of whole-body X-irradiation with doses of 1000, 1500 and 2000 r combined with surgical trauma. Wounds 2.5 cm long were inflicted on nonanesthetized rabbits. The course of radiation sickness was most severe in the animals operated on 3 hours after irradiation. If the wounds were inflicted 24 hours after irradiation, they did not aggravate the radiation sickness. Of 33 rabbits operated on 3 hours after irradiation, 4 survived; of 32 operated on 24 hours after irradiation, 8 survived. The wounds that were inflicted just before or after irradiation not only had no unfavorable effect but, according to the author, even mitigated the course of the radiation sickness.

V. B. Zakharzhevskiy (1960), in experiments on cats, combined whole-body X-irradiation with a dose of 400 r and functional trauma of the central nervous system. The trauma was caused by so-called electric interference, i.e., passing an electric current through the body of an animal while it is eating. If the irradiation was carried out from 3 to 30 days or just after the interference, the severity of the sickness increased considerably, as did mortality. However, if the cats were irradiated within 1 hour or 24 hours after the trauma, radiation sickness was milder than in the animals that were only irradiated.

V. I. Popov et al. (1960) exposed rats to whole-body irradiation with a dose of 500 r and induced shock by electric stimulation of the sciatic nerve and venesection. In the latent period of radiation sickness, the animals were rather resistant to shock-inducing agents, but shock was easier to induce at the height of the sickness.

During the recovery period, the reactions of the irradiated animals were the same as in the intact animals. Investigations of the bioelectric activity of the autonomic nuclei of the hypothalamus, reticular formation and cerebral cortex likewise confirmed the existence of differences in the development of shock in relation to the time elapsing since irradiation. There are times after irradiation or after inflicting a wound when the effect of two injurious agents is less than each of them applied separately. However, time is not the only factor responsible for the effect of the additional trauma, and the reasons for the differences and, sometimes, for the diametrically opposite results of combined action are still obscure. /9

Other cases have been described in which the effect of irradiation combined with other injurious factors was no stronger and, at times, was even weaker than each factor separately.

Carker and Close (1962) exposed mice to explosive decompression (the abstract from which this reference is taken does not mention the parameters) soon after a semilethal dose of whole-body irradiation. The mortality rate did not significantly exceed that of the group exposed to decompression alone.

A. D. Zurabashvili et al. (1958) investigated the effect of a closed skull injury and whole-body irradiation with a dose of 500 r in dogs. The injury caused a prolonged stupor, loss of appetite, impairment of motor function, and increased leukopoiesis of bone marrow. Morphological changes in the central nervous system were similar to those observed after a shock wave. Irradiation alone produced a typical acute radiation syndrome. After the combined insults, according to the authors, the clinical symptoms of radiation sickness were less pronounced than in animals exposed only to irradiation, and the structural changes in the nervous system were more moderate. In only a few instances was there an intensification of the symptoms of radiation sickness (the abstract from which this reference is taken does not include the quantitative data).

A. N. Gamaleya et al. (1959) resected 20 cm of the ileum in anesthetized dogs 4-5 hours after whole-body X-irradiation with a dose of 600-650 r. The course of the postoperative radiation sickness was approximately the same in the groups exposed to irradiation alone or to the combined factors.

Ye. A. Kovalenko (1958) observed a combination of weakened effect of trauma and intensified effect of irradiation. He compressed soft tissues /10 of the femur with clamps for 8-9 hours. The result was generalized excitation of the animal, elevated arterial pressure, rapid pulse and respiration and increased oxygen consumption. Excitation later alternated with depression. The pressor reflexes decreased with impairment of the intensity relations. Functional tests indicated a diminution of the compensating capabilities of the cardiovascular system. After removal of the clamps, as the sensitivity of the compressed tissues was restored, marked excitation developed, followed by depression and death. Whole-body irradiation with a dose of 350 r 1.5-2 hours before application of the clamps mitigated the reaction to compression. The intensity of the vascular reflexes in these dogs changed less, and the phase phenomena were not as common. After the combined action, some of the animals (4 out of 20) survived, but in all survivors radiation sickness after removal of the clamps followed a more severe course and they died sooner than did the animals exposed to irradiation alone.

Thus, among the numerous studies on the mutually aggravating effect of two injurious agents we also find references to the lack of intensification of the injury, and even to mitigation thereof, in evaluation of the results from the total effect.

The mechanism of the combined action of radiation and other factors is a highly complex and little understood phenomenon, despite the fact that there is an extensive literature on the subject. According to the published experimental material, the following are the reasons for the change in radiation effect in the case of combined action:

- (1) change in oxidative processes in tissues (oxygen effect);
- (2) change in central nervous system function;
- (3) change in organ and tissue function;

(4) change in mitotic activity of tissues;

(5) change in regenerative and compensatory processes;

(6) interaction of the effects of irradiation and the additional factor on the individual reactions of the body. The influence of irradiation and the non-irradiation factor on the different processes may be manifested in the same or opposite direction.¹

These factors are far from exhausting the possible mechanisms of the combined action. But we shall comment on them, because the available experimental material is fairly abundant. /11

The oxygen effect has been the object of numerous investigations. Certain pharmacological agents that create hypoxia are used to provide protection against radiation. Discussion of this aspect is beyond the scope of our article. The oxygen effect is usually ascribed to the influence of hyper- and hypothermia on radioresistance of the animal organism.

We should like to mention here the work of M. M. Konstantinova (1961, 1962), because the hypothermia used by this investigator was itself an injurious agent, one that killed the animals, yet had a favorable effect on radioresistance. Konstantinova found that cooling the body of mice resulted in a mortality rate of 9.5 ± 6.56 percent at 18°, 65.2 ± 10 percent at 12° and 48.7 ± 8.7 percent at 6°C. After the mice were cooled to these temperatures, gamma-irradiation with a dose of 900 r caused a mortality rate of 90, 84, and 64 percent, respectively. Oxygen tension in the organs of the cooled mice was low.

The effect of nervous system function on radioresistance is pronounced. Although it has been intensively studied, much remains to be done. The clearest results were obtained by investigating the effect of functional trauma of the nervous system on radioresistance (Kurtsin, 1958a, 1958b, 1959, 1961; Karpenko, 1959; Pashkovskiy, 1959; Popkov, 1961; Popov, 1958; Chursin, 1958; others). In these experiments about 100 dogs were exposed twice to whole-body X-irradiation with a dose of 250-350 r.

A neurosis was induced in some animals before the first exposure; in others, before the second. Development of the experimental neurosis was verified in some of the animals by testing the conditioned reflexes.

The authors concluded that radiation sickness in animals with a functionally weakened nervous system is more severe than in those not exposed to additional factors. In the animals with an experimental neurosis, irradiation caused even more severe impairment of some functions of the digestive organs.

¹The six possible mechanisms of combined action are listed in this way for reasons of convenience in connection with the following discussion rather than in order of importance.

A. P. Myasnikov (cited in I. T. Kurtsin, 1961) inflicted functional trauma on the nervous system of cats shortly before whole-body irradiation with a dose of 600 r or an hour later. The method used was "electric interference", as in Zakharzhevskiy's experiments. Of 36 cats in which irradiation was combined with the trauma, 19 died 6-9 days later, but none of the 18 irradiated but nontraumatized animals died. /12

Change in nervous system function is apparently caused by intensification of radiation lesions when irradiation is combined with pain, but, unfortunately, gas exchange in the experimental animals was not controlled in any of the investigations known to us.

T. B. Movsenyan et al. (1962) stimulated rabbits three times with an electric current before irradiating them with a dose of 950 r and at various times thereafter. The animals exposed to the combined action had a more pronounced hemorrhagic syndrome and some other manifestations of radiation sickness. Of 10 rabbits exposed to pain alone, none died; of 10 irradiated rabbits, 3 died; of 10 animals exposed to the combined action, all died.

The relationship between this reaction and nervous system function has been analyzed by I. B. Bychkovskaya (1955). In experiments on mice she found that stimulation with an electric current (10 v) increased mortality and shortened the life span of animals exposed only to whole-body irradiation with a dose of 440 r. This effect occurred whether or not pain was applied--during, before or after irradiation. Pain without irradiation did not kill any of the animals. The same stimulation had no effect if the radiation dose was raised to 700-1000 r, but sharper and brief pain (with 40-50 v current) halved the mean life span of mice irradiated with 700 r. However, three hours of pain of the same intensity did not affect the outcome of radiation injury when the mice were stimulated for 2 hours before, during or 50 minutes after irradiation. Stimulation caused marked excitation, which was followed half an hour later by profound depression, at which time the animals were irradiated. The mice were also irradiated while in an excited state after brief stimulation.

Hall et al. (1962) found that brief electric stimulation at 2 min intervals over a period of 8 hours before X-irradiation with a semilethal dose had no effect on the mortality or length of life of mice, but the same stimulation applied after irradiation resulted in 100 percent mortality. Irradiation 2 hours after mice were delivered to the laboratory (from a farm 45 miles away) produced a higher mortality rate with a shorter mean life span than did the same irradiation carried out 48 hours after delivery. /13

Unfortunately, the authors did not specify the factors involved in delivery of the animals which affected their vulnerability to radiation, merely mentioning the "stress" reaction.

There is considerable experimental material on irradiation combined with pharmacological agents capable of altering nervous system function, the narcotics in particular. However, it is difficult to evaluate this material because of the complexity and diversity of the results of the pharmacological intervention. Such drugs often act on other processes at the same time,

specifically, gas exchange. Examination of these data does not come within the scope of this article.

Several investigations were aimed at elucidating the relationship between radiation effects and functional state of organs and tissues.

N. V. Sokolova (1962) reviewed the extensive literature and her own experimental findings on the subject. She was concerned with structural changes in the organs of animals irradiated in a state of relative rest and under the conditions of a functional load on a particular organ. The experimental animals were mice and guinea pigs irradiated with doses of 1000, 1200 and 1400 r. A functional load was placed on the kidneys by injecting diuretics--aminophylline and mersalyl. The animals were irradiated at the time of maximum diuresis. The life span of the experimental animals was shortened to one-third that of the control animals with normal diuresis. Morphological changes in the kidneys were much more pronounced in the experimental mice. The renal structures whose functions were excited by the drugs were selectively injured. To create a functional load on the liver, mice were injected with the cholagoges tansy and dehydrocholic acid. Pathomorphological changes in the liver were more severe in the experimental animals. Mostly the parenchymatous cells were affected in the mice given tansy, as compared with the reticuloendothelial cells in the mice given dehydrocholic acid.

A local load was placed on the lumbar segments of the spinal cord in guinea pigs by intermittent electric stimulation of the muscles in the hind leg under urethan anesthesia during irradiation. Mice were irradiated while swimming. In the guinea pigs, structural changes in the spinal cord were localized mainly in the segments connected with the muscles that functioned, whereas in the mice the spinal cord lesions were diffuse.

Mice irradiated while in estrus exhibited more severe morphological changes in the uterine mucosa than did the control animals. The first to die were 14 the dividing cells of regenerating epidermis.

Radiation injury is also more severe when the functional activity of an organ is increased after irradiation.

S. S. Vayl' and D. S. Sarkisov (1959) investigated gastric mucosa in cats after whole-body irradiation with a dose of 300 r under different feeding routines. Cats regularly fed once a day after irradiation with fatty food had no hemorrhages in the mucosa, whereas half the animals fasted for two days after the last feeding and then given a large portion of oatmeal with milk had multiple hemorrhages.

However, increased functional activity does not always aggravate the course of radiation sickness.

N. V. Sokolova and T. I. Gorshenina (1960) found that increased renal function after the administration of diuretics 24, 48 and 72 hours following whole-body X-irradiation of mice with a dose of 1400 r not only significantly increased the life span of mice, but prevented injury to renal parenchyma. Histological

impairment was pronounced in the renal parenchyma of the mice that were irradiated but not subjected to any other agent, but was almost imperceptible in the animals given diuretics after irradiation. This unexpected result (in view of the other data of these investigators) was due, according to the authors, to the fact that the diuretics administered after irradiation had a specifically therapeutic effect by detoxication of the organism.

The results of investigations in which animals were exposed to irradiation and strenuous muscular exertion are quite consistent with the view that radiation vulnerability is heightened in systems found in a state of intensified functional activity.

B. A. Markelov (1961) injected rats intravenously with Sr^{90} at the rate of 1 $\mu\text{Ci/kg}^*$ and made them run every day on a treadmill at 0.5 km an hour for 15 days. The running increased gas exchange 18-20 percent.

Mortality was 52 percent in the group of rats exposed only to irradiation for 60 days, whereas it was 100 percent among the animals subjected to the two factors.

S. N. Sergeyev (1960) subjected rabbits to physical exertion daily for several days after whole-body X-irradiation with a dose of 1000 r. The physical exertion involved running on a treadmill until exhaustion. Of the ¹⁵21 animals in this group, 14 died within 14 days of irradiation. Albuminous and fatty degeneration of the myocardium was pronounced in all.

Preliminary conditioning significantly increased the animals' resistance to the combined action of running and radiation. Mortality was much lower among the rabbits forced to run on the treadmill daily for 10-15 days before and after irradiation or only before irradiation: 1 out of 19 and 1 out of 15 rabbits, respectively. Myocardial changes were insignificant.

However, when moderate physical exertion is combined with irradiation, the results are different.

V. M. Pinchuk and E. I. Shcherban' (1958) subjected mice to moderate physical exercise--swimming for 30 min in water with a temperature of 25-30° just after whole-body X-irradiation with doses of 800 and 1200 r. After the combined action, just as in the experiments of other authors who combined irradiation with a functional load, degenerative changes in the organs of the mice were more pronounced than in the animals exposed to irradiation alone. The authors noted more extensive albuminous degeneration of the myocardium, fatty and albuminous degeneration of the liver and more severe destruction of hematopoietic tissue. However, regeneration set in sooner in the hematopoietic organs of these animals and their mean life span was longer.

E. I. Shcherban' (1960) found that moderate physical exercise during irradiation also had a favorable effect. She placed mice in a tank of water (heated to 25-27°) 1-2 sec before the start of whole-body irradiation and the animals swam about energetically while being irradiated with a dose of 1100 r for 3-4 min. The control mice were also in the water during irradiation, but

* μCi = microcuries

they were held fast and not allowed to exert themselves. Both course and outcome of radiation sickness were more favorable in the experimental mice than in the control. Of 50 mice in the experimental group, 25 survived for 48 days as compared with 14 in the control group (according to our calculations, these figures are statistically significant). The hematological indices were better in the experimental group. But after irradiation with 2200 r, mortality and length of life were the same in the two groups.

Similar results were obtained by L. N. Udgodskaya and Yu. G. Yudin (1957), who subjected rats to muscular exertion just before irradiation. They forced the animals to swim for 8-10 min in water (35-36°) with a 10 g weight tied to their tail. Immediately afterward the rats were irradiated with a dose of 750 r. Soon after irradiation, aplastic phenomena in hematopoietic tissue ^{/16} were more pronounced in the experimental animals than in the control. On the 12th day after irradiation, degenerative changes in the liver were also more marked in the experimental group. Later, the regenerative processes in bone marrow developed more rapidly in the experimental mice. The clinical symptoms of radiation sickness, according to the authors, were less evident in the experimental animals, and their mortality rate was somewhat lower than that of the control group. The lower mortality rate was not statistically significant, judging by our calculations based on the data included in this study, but the fact that the results of all three investigations coincide indicates that these data are fairly reliable. L. N. Mushinaya (1958) obtained similar results.

The favorable influence of physical exercise cannot be ascribed to the oxygen effect. In Shcherban's experiments, the oxidative processes in the animals during irradiation had to be high, especially since mortality decreased during irradiation under the influence of muscular exertion. However, the deceleration of metabolic processes during irradiation in those experiments in which the animals were forced to exercise before irradiation did not prevent degenerative changes from taking place in various organs. A more plausible assumption is that the favorable effect of physical exercise is due to intensification of the regenerative processes. L. V. Funshteyn (1961) also mentions this.

It is quite likely that this mechanism is not the only one. It seems to us that an important part must be played by intensification of the protective and compensatory capabilities of the organism, as a result of which moderate muscular work creates an optimal level of activity in many organs and systems, primarily the nervous and endocrine systems. There is as yet no direct experimental evidence to support this assumption.

The part played by mitosis in the effects of combined action is clearly revealed when irradiation and bleeding are combined. The loss of blood is an injurious agent, and if it is sufficiently extensive, it may have an unfavorable effect on the course and outcome of radiation sickness.

M. A. Movsesyan (1960) found that a loss of 50-60 percent of their blood killed 6 out of 10 intact rabbits. Bleeding carried out 1-2 days after whole-body X-irradiation with a dose of 800 r killed all 10 rabbits.

N. L. Beloborodova et al. (1962) investigated the effect of a loss of blood amounting to 1 percent of the body weight on hematopoiesis in a /17

group of rabbits exposed daily for 7 months to the isotope $\text{Fe}^{59}\text{Cl}_3$ with an activity of 10 μCi . Rabbits bled and exposed to the stable iron isotope and rabbits only bled served as the controls. Compensatory hyperplasia of the erythroid part of bone marrow, clearly pronounced in the control groups, was absent in the irradiated rabbits. The number of reticulocytes in the latter was smaller than in the control in both peripheral blood and bone marrow. The posthemorrhagic leukocytosis in the control animals was due to a rise in the number of lymphocytes and in the irradiated animals, to a higher neutrophil count. However, mutual aggravation after the combined action occurred only when the irradiation dose or the amount of blood lost reached a certain critical level.

V. A. Bondina et al. (1958) abstracted 40 percent of the blood of dogs 1-1/2 hours after whole-body X-irradiation. When bleeding was combined with irradiation (550-650 r), the clinical course of the radiation sickness was more severe, as shown primarily by the absence of a latent period. The same amount of bleeding after irradiation with a dose of 500 r had no significant effect on the course of radiation sickness and intensified the anemia only slightly. After irradiation with a dose of 400 r, bleeding had a favorable effect in the form of a somewhat earlier restoration of the functions of the erythroid series.

The stimulating effect of bleeding on regeneration of hematopoiesis, when combined with whole-body irradiation, was studied in detail by A. D. Pushnitsyna (1957, 1962). The earlier investigation involved bleeding rats immediately after acute whole-body X-irradiation with doses of 250 and 400 r. Some 25 percent of the total blood was abstracted. In rats exposed to the combined action, the weight loss was greater and the anemia more pronounced and persistent than after each of these factors applied separately. The number of reticulocytes increased after bleeding, but returned to the original level on the 10th day. Irradiation caused an initial drop in the reticulocyte count, which later slightly rose above the original level. In rats exposed to the combined action the reticulocyte count decreased, as it did in the irradiated animals, but the elevated count phase started earlier and was more pronounced.

The stimulating effect of bleeding on regeneration in the hematopoietic system is even more apparent when it is combined with chronic irradiation. /18
A. D. Pushnitsyna (1962) removed about 25 percent of the blood of rats before exposing them to chronic gamma-irradiation with total doses of 500 and 1000 r given over periods of 5 and 10 days.

Bleeding without irradiation increased the absolute number of erythroblasts in bone marrow almost 100 percent. Irradiation with 500 r over a period of 5 days reduced the number of erythroblasts by more than half. The number of erythroblasts in the bled and irradiated animals was the same as in the animals not subjected to any action at all. Bleeding had no effect on white marrow. Here the agents to be combined had the opposite effect on red marrow, but when combined the effects leveled out.

These studies show that bleeding has a double action on hematopoiesis in irradiated animals. It accelerates and intensifies radiation injury (Bondina et al., 1958) while stimulating the regenerative processes.

G. S. Strelin (1962) showed that the reason for this is that bleeding stimulates hematopoietic tissues to proliferate, which, of course, increases radiosensitivity, but at the same time it accelerates regeneration, which helps to overcome radiation injury more quickly.

M. F. Aleksandrova and L. N. Selivanova (1963) observed only the phase of intensified radiation injury to hematopoietic tissue with high mitotic activity.

They exposed 7 dogs daily to internal irradiation from Sr^{90} (daily dose 1.7 rad, total dose 400 rad). In 3 of the dogs, bone marrow function was low normal; in the other 4, high normal (the norm was determined in 15 control animals). In the dogs with low functional activity of hematopoietic tissue after 10 months of irradiation, the number of erythroblasts in bone marrow increased 37 percent above the original level, while the number of granulocytes fluctuated around the original level or slightly above for 7 months. The count dropped 35 percent only after 10 months of irradiation. In the animals with high functional activity of bone marrow, the granulocyte count dropped 35 percent within a month of the initial irradiation. This was followed for 3 months by activation of granulocytogenesis, but by the end of the observation period, the granulocyte count was 40 percent of the original level. These data, obtained from a small number of animals, were not statistically processed and they require verification. Nevertheless, they are grounds for believing that an increase in the mitotic activity of hematopoietic tissue intensifies its vulnerability to radiation.

However, a mass of experimental material indicates that the stimulation of proliferative activity not only hastens the development of radiation injury but frequently accelerates regeneration even more. /19

L. V. Funshteyn (1956) describes the favorable effect of the stain scarlet red, a stimulant of mitosis, on the course of radiation injury to skin. Rabbit ear was exposed to local X-irradiation with doses of 1722, 1800 and 3000 r. The stain was injected subcutaneously inside the ear, and, whether done before or after irradiation, it considerably mitigated the injury to squamous epithelium.

The same author (Funshteyn, 1957), to stimulate proliferative activity of the squamous epithelium, used naphthalan petroleum. Sections of animal skin and rabbit ear were subjected to local radiation of 1000, 2000 and 3000 r by means of Sr^{89} and P^{32} applicator.

Naphthalan petroleum destroys some epithelial cells, but causes the surviving epidermal cells to proliferate. When this substance was applied before or after irradiation, the course of radiation injury to skin was considerably mitigated as a result of accelerated regeneration of the portions of epithelium left more or less uninjured by irradiation.

This was also the finding of I. V. Shiffer (1957), who investigated the relationship between radiation injury to corneal epithelium and degree of mitotic activity therein. Cell division was most active in the upper part of the cornea, but diminished downward. In mice and rats, the cells divided more vigorously on the periphery of the cornea and were least active in the center. Local irradiation of the eye with doses of 700, 900, 1800, 3600, and 7200 r caused lesions that became evident first in the zones with the highest proliferative activity. Tissue regeneration also started first in these zones. A spot burn in the cornea stimulates proliferation. Such a burn inflicted at different times after irradiation of the cornea hastens the onset of radiation injury while intensifying the rate of regeneration, thus producing a more favorable outcome.

The effect of various stimulants of proliferation on the course and regeneration of radiation injury to tissues was found to be the same in some other investigations conducted in the laboratory of G. S. Strelin, which we will not consider here. They all confirm Strelin's explanation of the mechanism of action of bleeding on hematopoiesis. But bleeding affects not only the proliferative activity of hematopoietic tissue, but many other functions as well.

The detailed investigations of V. F. Cherkasov (1958a, b) demonstrated that blood loss can favorably affect the course and outcome of radiation /20 sickness even under conditions in which this agent does not materially change hematopoiesis. The author abstracted 14-15 percent of the blood of cats 60-90 min after whole-body irradiation (400 r). The cellular composition of the peripheral blood of cats subjected to the combined action did not differ significantly from that of the irradiated control cats. After irradiation and bleeding, impairment of reflex regulation of the blood circulation and respiration was deeper than after irradiation alone. The depressor effect decreased after stimulation of the peripheral segment of the vagus nerve in both groups of animals, but impairment of the intensity relations occurred sooner, more frequently, and to a greater depth in the animals subjected to the combined action. A paradoxical phase was noted more often in this group. An investigation of the effect of stimulating the central segment of the vagus nerve on arterial pressure and the cardiac rate revealed that phasic phenomena were also more common in the animals subjected to the combined action.

The author observed similar phenomena when investigating accelerated respiration in response to stimulation of the sciatic nerve. They were four times more frequent in the animals subjected to the combined action than in the control that was just irradiated.

Furthermore, bleeding significantly reduced the mortality rate: 12 percent of the animals that were only irradiated survived, as compared with 30 percent of those subjected to the combined action.

The author suggests the following possible mechanisms of the combined effect: change in functional load of the cardiovascular system, reduction of the oxygen supply, excitation of the sympathetic adrenal system and stimulation of the defense mechanisms. Evidence for the last possibility is provided by the fact that reactivity to additional bleeding was higher in the cats subjected to the combined action than in the control.

I. R. Petrov (1962) states that an additional trauma mobilizes the compensatory forces of the irradiated organisms, thereby preventing aggravation.

In the works discussed above, we encountered phenomena reflecting the interaction of the effects of irradiation and trauma on individual reactions.

These investigations are worth comparing with our experimental data, despite the fact that both largely describe the phenomena rather than elucidate the mechanisms of these reactions.

According to the literature, the following cases are possible:

1. The reactions provoked by irradiation and another agent are in the same direction. Reciprocal intensification of the effects is possible, but there can also be a lack of summation, decrease or complete distortion of the effects. /21

2. The reactions provoked by irradiation and another agent are not in the same direction. Cases have been described of an unusual "algebraic summation" of the effects to the point of complete disappearance or partial predominance of the effect of one of the factors somewhat reduced by the other agent. Sometimes one of the agents is completely dominant. There are also cases where the reaction to one of the agents is intensified by the other, even though its action is diametrically opposite. Also, a combined action may be followed by peculiar reactions that differ markedly from the effects caused by the separate action of each of the factors.

Particular attention has been paid to the effect of combined action on the hematopoietic system. Irradiation was generally combined with an agent capable of causing leukocytosis in intact animals. Many studies describe a mitigation of leukopenia after combined injuries.

The authors who clearly demonstrated that radiation and nonradiation injuries aggravate one another, like the authors who did not observe this phenomenon, found that radiation injury to blood was mitigated when a trauma of nonradiation nature was inflicted.

S. S. Sokolov (1956) observed that the leukocyte count dropped more slowly and restoration of the original count occurred sooner in guinea pigs exposed to whole-body X-irradiation and a skin-muscle trauma than they did in animals that were only irradiated. In the animals subjected to the combined action, the leukocyte count in the restoration phase exceeded the original level, but it merely reached this level in the animals that were only irradiated.

In rabbits in which the radius was resected 30 min after whole-body irradiation (600 r), leukopenia was less pronounced than in the animals that were only irradiated (Blinov, 1958).

Sh. R. Topuriya et al. (1959) likewise found that when a shock wave was combined with whole-body X-irradiation (300-400 r), changes in the hematological indices of dogs were less marked than after irradiation alone. The drop in

leukocyte and reticulocyte counts after the combined action was less substantial and regeneration started sooner and was more pronounced. In the overwhelming majority of cases, mitigation of the blood reactions to irradiation after the combined action has no significant effect on the course and outcome of radiation sickness. After a combined action, the weight loss of animals is greater, despite the milder impairment of the hematopoietic system (Gamaleya et al., 1959; Blinov, 1958; others). /22

Cases have also been described in which irradiation combined with an agent that causes leukocytosis intensified the resultant leukopenia.

N. N. Aleksandrov et al. (1962) noted that in rabbits subjected to whole-body irradiation (600 r) and skull injury, the leukocyte count in peripheral blood was much lower than in animals that were only irradiated. In the experiments of V. A. Suvorov and B. A. Saakov (1960), a burn inflicted on dogs 5-6 days after whole-body X-irradiation (500-600 r) intensified the leukopenia that had developed by that time.

M. I. Ul'yanov and B. V. Sakharov (1963) investigated the leukocyte reaction to pain in dogs after whole-body X-irradiation with doses ranging from 3 to 600 r. In intact dogs, moderate pain (pricking or scarification to draw blood) provoked a redistributive leukocytosis. After irradiation the same stimulation resulted in a leukopenic phase. Following the inflicting of a wound (fracture of the knee joint), the reaction to additional pain was only an elevated leukocyte count. In some instances the authors observed that dogs subjected to the combined action of irradiation and trauma also developed the leukopenic phase of the reaction to pain, and it was more pronounced than after irradiation alone.

Ye. N. Ryumina (1962) abstracted rats' blood equal to 1 percent of body weight 24 hours after administering the isotope Na^{24} with an activity of 0.25 μc . Bleeding caused leukocytosis, whereas irradiation had no effect on the total leukocyte count. The combined action was followed by a leukopenia similar to that resulting from irradiation with higher doses.

The reasons for the difference in action of an additional trauma on the radiation reaction of the blood system are still obscure.

We conjectured that there might be a relationship between the effects and the intensity of the agents used. To check this assumption, we compared the experimental results of a number of authors, but could find no evidence of such a relationship. Special investigations will obviously have to be undertaken to solve the problem.

K. F. Tovstoles (1963) describes a clear mutual aggravation of renal dysfunction following renal trauma combined with whole-body irradiation with doses of 400, 600 and 800 r, although the reactions to the isolated action of each of the factors were not always in the same direction at all the stages.

TABLE 1. COMBINED ACTION OF WHOLE-BODY IRRADIATION AND A BURN ON SOME INDICES OF EXCITABILITY OF THE SYMPATHETIC AND PARASYMPATHETIC SYSTEMS, ACCORDING TO V. A. SUVOROV AND B. A. SAAKOV (1960).

Type of action	General condition of animal	Leukocyte count	Arterial pressure	Reaction to administration of lobeline		Pressor reaction to administration of epinephrine	Depressor reaction to administration of pilocarpine
				Increase in amplitude of respiratory movements	Pressor reaction		
Burn	Excited	Insignificant leukocytosis	Elevation	High	High	High	High
Irradiation	-	Leukopenia	Drop of 10-30 mm Hg	Insignificantly high	Low	Almost unchanged	Unchanged or slight decrease
Irradiation + burn	In many cases shock without erectile phase, fatal outcome	Intensification of leukopenia	Further drop of 33 mm Hg	Low	Very low	Low	Very low

In rabbits that were only irradiated, the amount of urine the first ^{/23} day rose slightly, but decreased 90 percent starting the third day. The trauma reduced the output of urine by 50 percent in a week. After the combined action, the amount of urine decreased 50 percent the very first day.

There was no delay in excreting a dye (indigo carmine) after irradiation. Following the trauma, impairment of this function was recorded for two weeks; after the combined action, for a month.

Interesting kinds of effects of a combined action are described by several authors.

V. A. Suvorov and B. A. Saakov (1960) investigated the effect of burns and whole-body X-irradiation with 500-600 r on the electroencephalogram and some indices of excitability of the sympathetic and parasympathetic nervous systems in dogs. A burn was inflicted 5-6 days after irradiation on the lower part of the abdominal wall and inside of the thigh. The results are shown in table 1.

It is evident from the table that, according to some indices, the reactions to the burn and irradiation were in different directions. Nevertheless, the effect of irradiation was intensified by the combined action. In those cases where the authors were unable to detect a clear-cut reaction to irradiation (pressor effect of epinephrine and depressor effect of pilocarpine), ^{/24} while the reaction to the burn was pronounced, the reaction to the combined action reversed direction--instead of the excitability of the sympathetic and parasympathetic systems intensifying, it decreased. A burn alone resulted in the development of the erectile phase of shock, which did not turn into the torpid phase even once over a period of two hours. A burn inflicted after irradiation caused severe burn shock without the erectile phase.

TABLE 2. EFFECT OF IRRADIATION, ELECTRIC INTERFERENCE AND COMBINED ACTION OF BOTH FACTORS ON THE SIZE OF THE THRESHOLD DOSE OF POTASSIUM CHLORIDE THAT CAUSES CHANGES IN ARTERIAL PRESSURE AND RESPIRATION UPON PERFUSION OF PART OF THE INTESTINE (ZAKHARZHEVSKIY, 1960).

Group of animals	Time after action	Mean threshold dose of KCl, mg		
		After irradiation	After interference	After combined action
Experimental	1-5 hours	4.6	11.3	15.5
	1 day	15.6	6.3	17.1
	3 days	20.1	3.7	15.2
	7 days	20.7	15.2	24.2
	10 days	-	21.8	-
	14 days	18.0	12.6	14.9
	21 days	23.2	5.4	12.7
	30 days	10.2	3.1	30
Control	-		4.3	

An interesting quantitative comparison of the results of combining irradiation with functional trauma of the nervous system is included in the study of V. B. Zakharzhevskiy (1960). As mentioned before, this author inflicted a functional nervous system trauma on cats by combining electric stimulation with eating, "electric interference." He investigated in the same animals reflex changes in respiration and arterial pressure after stimulating the chemoreceptors of the perfused part of the intestine.

This part of the intestine retained only a nerve connection with the organism (table 2).

A statistically significant difference was noted between the groups subjected to the combined action and to radiation alone only during the first few hours and on the third day after the action. But the data of the other 25 times are also of great interest.

It is evident from the table that the effects of irradiation and interference were always in the same direction. In both cases the thresholds were high, but the dynamics of the changes after interference and radiation were different.

The threshold dose after the combined action from the first few hours through the 7th day inclusive was the maximum with the separate action of each of the factors, i.e., at first the influence of interference was predominant, then the influence of irradiation. On the 21st day the threshold dose after the combined action was almost exactly equal to the arithmetic mean of the doses established after the action of each factor separately. The same phenomenon occurred also on the 14th day, but the difference between the values being compared was too small on this day to attach any significance to the effect. Finally, on the 30th day the threshold after the combined action was 3 times higher than the maximum threshold observed at this time after the action of one of the factors. This shows how the effect of combined action changed in a single group of experiments. At different times there was now the alternate predominance of each component, now the weakened action of one of them (irradiation), now its sharp intensification. In the last two cases (on the 21st and 30th days after the action) the isolated use of "electric interference" did not change the parameter under investigation.

The combined action of ionizing radiation and the dynamic factors of interest to us (acceleration and vibration) have been studied very little.

A. N. Ganshina (1961) investigated the combined action of vibration and whole-body irradiation (400 r) on the microscopic structure of tissues from the aorta, heart, lungs, liver, small intestine and spleen of rats. The author used vertical vibration with a frequency of 70 cps and an amplitude of 1 mm over a period of 4 hours 4 times every other day. This powerful action caused hyperemia in the organs and, in some cases, pulmonary hemorrhages. The combination of vibration and acute whole-body irradiation (400 r) intensified histological changes in the organs of rats irradiated without exposure to an additional action. The hemorrhages were particularly pronounced after the combined action. This did not happen, however, when vibration was combined with fractional irradiation.

Taylor (1960) found no difference in tolerance of centrifugation with an acceleration of 20 g as between rats irradiated with 600 r just before the action and intact animals.

Lyle (1961) likewise failed to detect changes in tolerance of acceleration in rats with polycythemia induced by whole-body gamma radiation. /26

K. V. Ivanov et al. (1962) showed that rotation on a centrifuge at a speed of 200 rpm for 26 min during whole-body X-irradiation increased the radioresistance of rats. In rats centrifuged during irradiation with a dose of 1000 r, the length of life was somewhat longer and the loss of weight less than in animals irradiated without exposure to another factor. These experiments, modified slightly, were repeated by Ye. S. Meyzerov and the author of this article.

We subjected mice to radial accelerations of 10 g for 15 min by rotating them in a centrifuge for 10 min before whole-body irradiation with a dose of 500 r. The mortality rate was lower in the mice subjected to acceleration before irradiation and the changes in total leukocyte count were less pronounced than in the mice that were only irradiated.

We think it quite likely that there is a relationship between the action of acceleration and the oxygen effect, because impairment of the hemodynamics by centrifugation creates conditions conducive to hypoxia.

Our brief review of the literature shows how varied the effects of combined action may be. This variety is apparently due to the heterogeneity of the mechanisms responsible for these effects. We were able to examine the participation of only those physiological mechanisms which were specifically investigated and on the influence and importance of which there are quantitative experimental data. Therefore, such a significant factor as change in the humoral background after combined radiation injury was not considered, even though there are theoretical reasons for expecting it to be of great significance (Khromov, 1959). Furthermore, little attention has been paid to the effect of additional injury on the mechanism of the compensatory processes. Thus, our knowledge of the mechanisms of combined injuries is still quite incomplete and this makes the interpretation of our experimental data difficult.

All these mechanisms may be expected to play a part in the combined action of vibration and irradiation.

1. It has been shown that under the influence of vibration the oxidative processes, especially in brain tissues, are intensified during the action and undergo phasic changes in the aftereffect. Accordingly, regardless of the time after vibration that irradiation is carried out, the effect of the latter may be strengthened or weakened under the influence of the oxygen effect.

2. Vibration brings about major changes in nervous system function, as revealed by the literature and our own experiments (compare the articles of Z. I. Apanasenko, M. A. Kuznetsova and L. D. Luk'yanova in this collection). Changes in nervous system function due to vibration are so sharp that they must be expected to assert a marked influence on radiation reactions. We /27

believe that these two mechanisms play a major role in differentiation of the results of the experiments performed by L. D. Luk'yanova, Z. I. Apanasenko and M. A. Kuznetsova.

Luk'yanova carried out irradiation for 10-15 min after vibration, following depression of the oxidative processes in brain tissues and parabiosis of the central nervous system. She observed that the effect of vibration was distinctly protective.

Apanasenko and Kuznetsova irradiated animals somewhat later--30-40 min after application of vibration. In their experiments the radiation injuries after the combined action were more severe. The animals died 1-2 days sooner than those subjected to irradiation alone.

3. The functional state of organs and tissues changes under the influence of vibration. Specifically, as Apanasenko showed, the bioelectric activity of the skeletal muscles after vibration remains high for at least 10 days. We have as yet no data that would enable us to determine how this effect influences the radiation reactions of the organism. Presumably, there are some analogies here with the effect of light muscular work. It is now generally known that the effects of radiation on electric activity of muscles is considerably altered by vibration.

4. Bone marrow cells, as Yu. S. Demin shows (see his article in this collection), are sensitive to vibration. We still do not know, however, whether the course of regeneration in hematopoietic tissue is affected by vibration.

The physiological studies included in this collection show that all the investigated nervous system reactions to irradiation are significantly altered by combined action. This aspect has received more attention than the others.

Apanasenko, Kuznetsova and Luk'yanova investigated those CNS functions on which vibration was expected to have the greatest effect. This agent is, to a certain extent, an adequate stimulus for the vestibular and motor analyzers. In point of fact, the intensity of the effect of vibration on the latent period of the unconditioned motor defense reaction was equivalent to that of a lethal dose of radiation, although this index is known to be extremely sensitive to radiation (Kudritskiy, 1957). Changes in some of the characteristics of the vestibular-tonic reflexes under the influence of vibration were fairly substantial. Vibration also had a very pronounced effect on the oxidative processes in brain tissues in the central portion of the motor analyzer and motor nuclei of the subcortex (changes in tension of free oxygen and in its rate of utilization in the auditory regions of the cerebrum are not too characteristic because they might have been caused by the noise generated by the vibrating stand). Therefore, it is not surprising that vibration was the more dominant element in the combined action of the two factors on the reactions investigated. This dominance was most apparent after the action of vibration and irradiation on the background bioelectric activity of the skeletal muscles in the early stages of changes in myoelectric activity after stimulation of the vestibular analyzer, in the aftereffect of this stimulation and after change in duration of the aftereffect. Similar patterns have been observed in the oxidative

processes in brain tissues where for the first few hours after combined action they scarcely differ from those in animals subjected to vibration alone. Only sometime later, as acute radiation sickness develops, the effect of irradiation begins to prevail in the dynamics of changes in the indices under study to the point where the effect of vibration becomes indiscernible. This was particularly evident in cases where the effects of irradiation and vibration were in different directions, i.e., after change in duration of the aftereffect on the test stimulus (compare Apanasenko's article).

Study of the effect of these factors on the latent period of motor defense reflexes showed that there were groups of animals in which the effect of irradiation was predominant and other groups in which the effect of vibration was predominant. It is still impossible to say whether these reactions are due to differences in radiosensitivity among the animals. A close resemblance to the reaction to irradiation was found only in changes in the thresholds of excitability of these reflexes after combined action.

In the case of unidirectional action of both factors in our investigations, summation of the effects was an exception rather than the rule. Yu. S. Demin performed a great many experiments on the combined effect of irradiation and vibration on chromosomal adhesion, and in only three instances did he find significant summation: 30 min and 5 hours after the application of vibration followed by irradiation with a dose of 100 r, and 5 hours after the application of vibration followed by irradiation with a dose of 50 r. Two days after the combined action of vibration and 100 r of radiation the effect was insignificant, although slightly greater than that of vibration alone, as was the case 24 hours after vibration and irradiation with 50 r. In 13 other counts, the number of chromosomal adhesions was either equal to the isolated action of one of the factors or, more often, was somewhat less. The number of chromosomal aberrations after the combined action was fewer than in the animals subjected to irradiation alone, even though irradiation increased the number of irregular mitoses of this kind, whereas vibration had no significant effect on them. /29

Luk'yanova investigated the absence of mutual intensification of the effect of vibration and irradiation on the course of the oxidative processes in brain tissues, despite the fact that both factors acting separately changed these functions in one direction. The author says, by way of explanation, that in her experiments irradiation was carried out against a background of protective inhibition, that followed the application of vibration and the ensuing depression of the oxidative processes.

This view was confirmed by Kuznetsova and published reports as well as by the preliminary experiments of the author of this article. We subjected rats to vibration under the conditions described in the articles of Apanasenko, Kuznetsova and Luk'yanova. A conditioned-reflex stereotype was formed and firmly stabilized in the animals. After exposure the rats exhibited inhibition of the conditioned reflexes with distinct hypnotic phases. Specifically, a complete ultraparadoxical phase was observed in one of the animals when conditioned reflexes to positive stimuli were absent, and it responded with a clear-cut food reflex only to differentiation.

Vibration combined with irradiation has a peculiar effect on the bioelectric activity of skeletal muscles and on vestibular-tonic reflexes (Apanasenko).

Irradiation causes a sustained drop in muscle bioelectric activity of the extremities, whereas vibration temporarily increases it. But combined action of the two also increases it. However, the dynamics are so similar to that after irradiation, that the curve reflecting the changes in this parameter is very similar to the mirror image of the corresponding curve in the irradiated animals. There are no references to such phenomena in the literature we reviewed.

Apanasenko showed that irradiation decreases the effect of vibration on the days when it is strong, but intensifies it when it is weak.

On the day of the first examination after the application of vibration, the background electric activity of the muscles was the highest, but after combined action this index was much lower. On the seventh day after vibration, electric activity was not very high, but after combined action it was close to the maximum value. Apparently the intensity of the additional action also has a bearing on the effect, which accounts for the mirror resemblance of the ^{/30} dynamics of changes in the aforementioned indices after combined action to that in the animals exposed to only one of the factors.

Similar phenomena were also observed when investigating the combined effect of these factors on muscle bioelectric activity following stimulation of the vestibular apparatus. Here, however, the relations were the reverse. Vibration decreased the bioelectric activity of the muscles, whereas irradiation increased it. The vibration effect predominated during the first two days, as was repeatedly observed, and after the combined action the index under study changed in the same direction as after vibration alone. On the third and fifth days after exposure, the electric activity of the muscles changed in the same direction as in the irradiated animals, but here the weak changes caused by irradiation under the influence of vibration became strong (third day) while the strong changes became weak (fifth day). These relations are very reminiscent of the phenomenon of dominant and parabiosis.

There are some references to this in the literature.

It was experimentally demonstrated that when irradiation is combined with factors that exert a directly opposite effect, the typical radiation reactions are intensified. For example, the agents that cause leukocytosis when combined with irradiation sometimes intensify leukopenia (Aleksandrov et al., 1962; Suvorov and Saakov, 1960; Ul'yanov and Sakharov, 1963; others). Irradiation combined with a burn causes changes in arterial pressure and in excitability of the depressor, pressor and other reactions similar to parabiogenic phenomena, as mentioned above (Suvorov and Saakov, 1960).

We still do not know whether we are dealing here only with an external change resemblance between these phenomena and those of parabiosis, or whether these mechanisms play an important role in combined radiation lesions. This matter requires experimental verification.

Besides these facts, we saw other quantitative patterns in the results of combined radiation actions.

In the experimental data of Yu. S. Demin presented in tables 1, 6 and 7, there is no direct relationship between the increase in number of irregular mitoses under the influence of each factor separately and the degree of reduction of the effect. Nor do we find any such pattern in the experiments of Luk'yanova or in those of other investigators.

It will be recalled that V. B. Zakharzhevskiy (1960) observed weakening of the reaction to the combined effect at the time when the influence of the additional factor ("interference") was least evident. This indicates that the /31 parabiologic processes need not be the only mechanism for weakening the effects after combined action.

We consider Luk'yanova's explanation of the lack of summation of the effect of irradiation and vibration on the oxidation processes in brain tissues quite plausible. This mechanism may also play a part in the phenomena described by Demin. This subject should be specifically investigated.

During investigations of functions on which irradiation and vibration have an opposite effect, in addition to the phenomena of dominance, cases were observed in which the effect of combined action was intermediate in intensity between the reactions to each of the factors separately. We encountered this phenomenon a number of times as we reviewed the literature.

Kuznetsova described an extreme manifestation of this type of interaction. Irradiation in her experiments led to lengthening of the latent period of the motor defense reaction to a weak stimulus, whereas vibration tended to shorten it.

The mean value of this index did not change after combined action. Similar relations were observed by A. D. Pushnitsyna (1962) when investigating the combined effect of irradiation and bleeding on the number of erythroblasts in bone marrow. Despite the apparent simplicity of this phenomenon, its mechanism is still obscure.

We see that the effects of ionizing radiation combined with vibration on the various functions studied are complex and diverse. This is probably due to the variety of the mechanisms of combined radiation lesions. Moreover, as we saw in our review of the literature, the results of combined action depend on a great many variables--intensity of each factor, time of application of the additional factor and individual peculiarities of the animal. The latter is clearly demonstrated in the work of Kuznetsova. However, we also found some common features in the reactions to the action of irradiation combined with vibration and with other factors. This convinced us that the many mechanisms of these reactions must have something in common, despite the completely different nature of the agents. Study of the mechanisms of combined radiation injuries is a very important task of future research.

EFFECT OF RADIAL ACCELERATION ON VENOUS FLOW
IN THE CEREBRAL BLOOD VESSELS OF RABBITS

V. Ya. Klimovitskiy

ABSTRACT

Blood flow in cerebral veins of 9 rabbits was studied by means of a thermistor coupled with a heater. Animals were exposed to accelerations of 5-10 g on the centrifuge in the direction "head-pelvis." Exposure for 30 sec was repeated 5-10 times with 30 min intervals for several days. Venous blood flow increased at the beginning of the centrifugation, and sharply decreased at the end. The phenomenon of successive reaction intensification during repeated exposure was recorded. After the centrifuge was stopped, the increase of venous blood flow during 3-5 min and a prolonged decrease afterward were observed. After 3-4 days some adaptation to the acceleration effect could be observed. It was found that the reaction of venous blood flow was determined by the interaction of 2 factors: passive mechanical blood displacement and physiological compensation.

Impairment of the cerebral blood circulation is one of the critical factors in man's tolerance of acceleration. The origin of such impairment is indirectly indicated both by the subjective condition of subjects in a centrifuge--visual disturbances, "black shroud," etc. (Barer, 1962; Kotovskaya et al., 1962)--and by certain objective data. /33

The significance of the passive mechanical factor in changes in systemic and cerebral hemodynamics after acceleration is still moot. There is some criticism of the hemodynamic theory of the effect of acceleration, but no one doubts the actual fact of marked changes in blood distribution and pressure in the vascular system.

There are references in the literature to the high resistance of cerebral hemodynamics to acceleration. For example, after acceleration of about 4-5 g in a fronto-occipital direction, arterial pressure "at the head level" in subjects fell to 10-15 mm Hg, while the cerebral blood flow, calculated from the arteriovenous difference in oxygen saturation of the blood, scarcely changed (Henry et al., 1951).

The stability of the cerebral blood flow despite a marked drop in systemic arterial pressure has also been noted. After gradual artificial lowering of arterial pressure in animals by abstracting blood, the cerebral flow remained within normal limits, and the cerebral flow did not decrease until arterial pressure was 30 mm Hg (Carlyle and Grayson, 1956).

Owing to the specific conditions of intracranial circulation, the venous flow apparently functions as an important regulatory mechanism of cerebral hemodynamics (Kedrov and Naumenko, 1954a, b; Kedrov et al., 1954). Venous pressure dropped in the jugular vein and jugular bulb simultaneously with a drop in arterial pressure "at the head level" in centrifuged subjects ^{/34} (Henry et al., 1951). This reaction may be aimed at partly normalizing the blood supply of cerebral tissues in this situation. The increase in venous flow and movement of fluid creates the necessary physical conditions for reducing cerebral vascular resistance (Moskalenko and Naumenko, 1957, 1959; Naumenko and Vasilevskiy, 1962).

The data on the lowering of arterial and venous pressures "at the head level" during centrifugation and information on the decrease in filling of the cerebral vessels with blood do not as yet fill out the picture of the cerebral hemodynamic changes resulting from acceleration. The cerebral flow scarcely changes until certain critical values of the action and duration of exposure are reached, but blood filling decreases appreciably after only 1.5-2 g or after a change of body position. Consequently, the start of acceleration is characterized by rapid evacuation of the "reserve" (apparently venous) blood from the cerebral vessels, followed by the establishment of an equilibrium between inflow and outflow until the critical values of acceleration are achieved. It is clear, then, that the reaction of the cerebral venous flow to acceleration is complex and multiphase. One of the purposes of our study was to investigate this reaction.

We also had to determine the critical values of acceleration and exposure and elucidate the dynamics of the responses to repeated loads. Thus, we tried to study the possibility of adaptation to acceleration and to model training processes in animals.

Method

Nine rabbits served as the experimental animals. Measurements were made with temperature-sensitive elements placed on the large veins of the brain surface in the parietal region or on the anterior transverse sinus.

The temperature-sensitive element was a tiny thermistor and contact heater straddling the blood vessel. The underlying principles are the same as those of the thermal sensors used to measure the volume rate of the blood flow as described in the works of several authors (Gibbs, 1933; Grayson, 1952; Linsell, 1953; Aschoff, 1957; Aschoff et al., 1957; Blinova and Ryzhova, 1958; Wetterer, 1962; Moskalenko, 1963).

We used our own modification of the Carlyle-Grayson method (1955, 1957), in which the amplitudes of temperature fluctuations on the thermogram are in inverse relationship to the blood flow rate. The emission of heat from ^{/35} the heater was in the form of individual heat impulses recorded as to time and intensity. One operating cycle of the sensor included heating (for one-third the duration of the cycle) and cooling. The cycle was set for 60, 20, 12 and 10 sec. It was not deemed worthwhile to shorten the duration any further because of the fairly high time constant of the "heater-blood-thermistor" system. A simplified calibration curve (fig. 1) was prepared in an acute experiment on the femoral vein of a cat and in a model where the sensor was placed on a steel needle. Water was passed through the needle. Figure 1 shows that the highest values of the blood flow correspond to the lowest points of the temperature peaks (and vice versa).

An enlarged thermogram of a cycle is shown in figure 2 (read from right to left). It was impossible to calibrate each individual sensor, because the diameter and shape of the blood vessel under study were unknown prior to the operation; the sensor itself was prepared during the operation, after the skull was trepanned. The distance between the elements of the sensor and their location were based on the size and shape of the blood vessel.

The curve showing the relationship between the heights of the temperature peaks (l_t) and flow F (fig. 1) is exponential and can probably be described by the equations $l_t = A e^{-\alpha F} + B$ or $l_t = \frac{A}{1+F} + B$ (the second equation is for ^{/36}

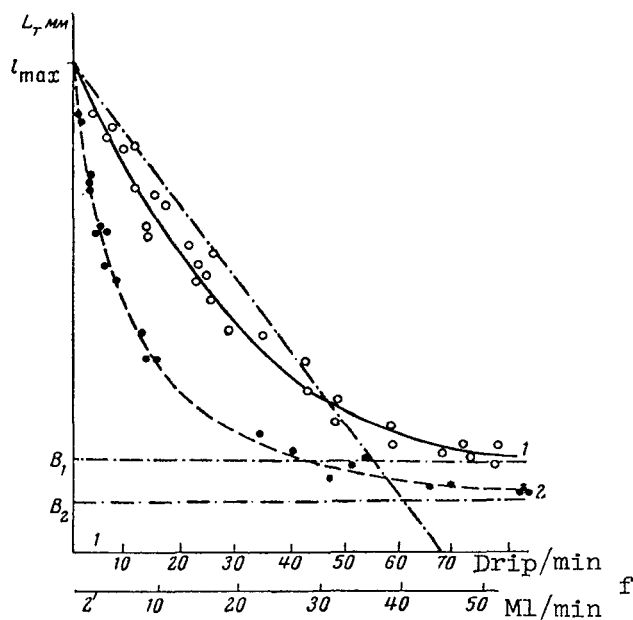


Figure 1. Calibration curves of heat-sensitive element, obtained on femoral vein of cat (1) and in model (2).

the case where the curve is close to a hyperbole), where A , B and α are constants. Both equations reflect the fact that when $F = 0$, we have the maximum value of l_t which, minus some constant B , is equal to the coefficient A ,

namely: $l_{t0} = l_{\max} - B = A$. The physical sense of value B is the following.

With comparable size of the elements of the sensor, on one hand, and of the vessel diameter, on the other, part of the heat flow from the heater will reach the thermistor in addition to the vessel. Therefore, when the flow rate is increased, the value of l_t will approach some constant B rather than zero. The curve bends down between the two values A and B , which are assumed by the function $l_t = f(F)$ when $F \rightarrow 0$ and $F \rightarrow \infty$, respectively. The value l_{\max} (obtained

from a dead animal) may be determined for each sensor. This makes it possible to solve graphically the equations for the sensor relative to F . If, as a very rough approximation, the initial part of the graph of the function which embraces the main working range of the values of F for the cerebral veins is regarded as a straight line, we obtain a qualitative solution relative to F from the equation of the straight line $F(l_{\max} - l_{\min}) - l_t F_{\max} = 0$. Here l_{\max} ,

l_{\min} , and F_{\max} are graphic values of the variables for the working range of the

values of F . A simple graphic solution is also possible. In either case, since it is difficult to calibrate each sensor, we deal with arbitrary units characterizing the integral value of the blood flow during a single heat cycle. We shall later designate these values as l_i in contradistinction to the abso-

lute values of the blood flow F . Thus, we repeat, each of the values of l_i

which we shall subsequently use reflects the value of the blood flow during a single thermal cycle in arbitrary units (here in mm because the equation was solved graphically).

It will be noted that with the proposed method of recording the blood flow rate we can compare the blood flow level not only for a series of reactions in the course of a single day, but for several days of the experiment. The sensor was secured surgically under sterile conditions. The dura mater was removed from within the round trepanation opening. The bone defect was

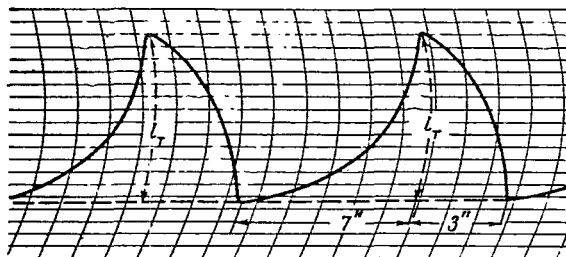


Figure 2. Enlarged thermogram of heat cycle, 3 + 7 sec.



Figure 3. Position of animal in centrifuge.

replaced with the frame of the sensor and the skull was hermetically sealed. The animals were used in the experiment up to 3-4 weeks. By this time the sensor was overgrown with connective tissue, which affected its sensitivity to blood flow changes, but the dynamics of these changes could be traced even at later times.

There were several versions of the recording and measuring apparatus. In all cases the thermistor functioned in a bridge scheme, while the thermal cycle was controlled by a multivibrator accurate to 0.01. The final recording of the process was carried out on an H-373 strip-chart recorder or on an EPP-09 automatic balanced bridge.

The animals were exposed to radial acceleration in a small-arm centrifuge with a constant cycle of revolutions. Acceleration of about 5 g developed in the head region while the pelvis was exposed to acceleration of about 10 g.

During the experiment the animals were held secure in harness fastened to the loading platform of the centrifuge at many places (fig. 3). Above the platform with the animal was a plexiglas chamber, the back compartment of which was filled with finely porous rubber to prevent the animal from shifting in the direction of the centrifugal force. A soft muzzle was drawn over the rabbit's head and connected to the platform of the centrifuge with rubber bands. The latter were not taut, but they prevented the animal from raising or turning its head to the side. The standard action was centrifugation for 30 sec at 30 min intervals. This dose was readily tolerated by all animals, even when repeated frequently, but 2-3 min action was fatal to most of them. /38

At the end of some experiments, the action was sustained for 60 sec to obtain gradation of the reactions to two stimuli of different intensities. Centrifugation was used a total of 90 times. In processing the material, we took as the zero level the mean value of the original resting level (background) before each exposure. The mean was obtained from a half hour recording of the blood flow at rest before the first whirling of the centrifuge, but before the

subsequent whirlings the mean values were obtained from the 10 min segment of the thermogram just before the centrifuge was started. The latter was necessary to avoid, as much as possible, obtaining the means not from the resting level, but from the "aftereffect" of the reaction to the preceding action of the centrifuge.

We regarded those changes as significant which were no smaller than the statistical error (m).

The blood flow was also investigated in 9 control animals not exposed to acceleration.

To determine the phases of the reaction, we used "run tests" (Siegel, 1956) as the criterion. The tables compiled furnished boundary values beyond which the presence of changes was significant at the 0.05 level. The boundaries of the phases were determined as the times when the function under investigation passed through the zero level.

Results

The mean values of the blood flow at rest obtained for a day changed from day to day during the experiment. These changes lay in a range of ± 10 percent of the mean level for the entire observation period. The distribution of the mean daily values around the mean for the entire experiment was random. During 2-6 hours of the experiment with repeated exposures to acceleration, the "resting" level between the exposures gradually dropped a little. However, the same thing happened in the 9 control animals that were not subjected to centrifugation.

As mentioned before, the recording of the blood flow consisted of a series of temperature peaks (fig. 4). The curve shown in figure 4 is a recording of the blood flow made on a tape recorder of the "automatic balanced recording bridge" type. The amplitudes of the temperature which integrally characterized the blood flow for 10, 12, 20 or 60 sec formed a series of values randomly distributed around a mean (according to the "runs test" criterion). The fluctuations in blood flow had a definite periodicity of 1.5-2 min that could not be detected by the runs test criterion. Sometimes these oscillations were completed more quickly (1.0-1.2 min). We observed this acceleration of fluctuations in trained animals. Under normal conditions (at rest) we never observed prolonged deviations of the blood flow from the mean level (more than 1.5-2.5 min). /39

Reaction of the Venous Flow to Acceleration

Prolonged and repeated exposures were followed in most cases (68 out of 90) by a more or less pronounced decrease in venous flow amounting to 90 percent or more of the original resting level. The value of this negative change greatly exceeded triple σ (fig. 5a and b).

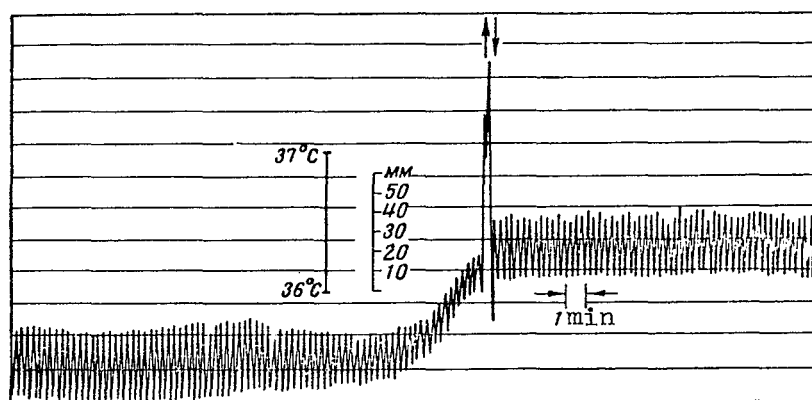


Figure 4. Thermogram of blood flow during centrifugation. Rabbit No. 57. Scanning from right to left. Arrows indicate switching on and off of centrifuge motor (duration of action 30 sec).

The level of deviations from the mean ($= 3 \sigma$) is indicated in figure 5a-c by a broken line. The arrows indicate the switching on and off of the centrifuge motor. The initial actions the first day of the experiment on an animal that had not previously been subjected to centrifugation invariably elicited a weak reaction whose direction was only positive. The subsequent reaction usually consisted of two or three phases, one of which was positive.

A typical series of reactions to several exposures on one day is shown in figure 6. The diagram reflects deviations of the blood flow values from their mean under normal conditions (in percent) in one of the experimental animals. Each group of values is the result of a single centrifugation, and each of the values reflects the deviation from the mean of an individual temperature peak lasting 20 sec. The figures above indicate the length of time the motor ran in seconds and the interval between exposures in minutes. /40
The data in the diagram were obtained on the second day of the experiment. The day before, this animal was centrifuged 7 times. It is evident from figure 6 that the reaction to acceleration generally starts with a slight decrease in the venous flow. This stage can be regarded as the integral result of a more complex reaction. The initial passive mechanical return flow of venous blood could not be detected because it was too fast. It was followed by a slight decrease in blood flow in the vessel under study, which is reflected on the experimental curve by an increase in the first thermal amplitude. The regular presence of a phase of intensified venous flow is noteworthy. Almost all the deviations of the second peak (after the start of acceleration) were positive. Finally, a stage of marked decrease in blood flow set in. The predominant change was generally negative. Hence, the mean change was negative in most cases (in 68 out of 90). /41

The decrease in blood flow, if any, persisted until the centrifuge was halted. The motor ran 30 or 60 sec, and 30 more sec were required for the centrifuge to come to a complete stop. Restoration of the blood flow then began promptly. /42

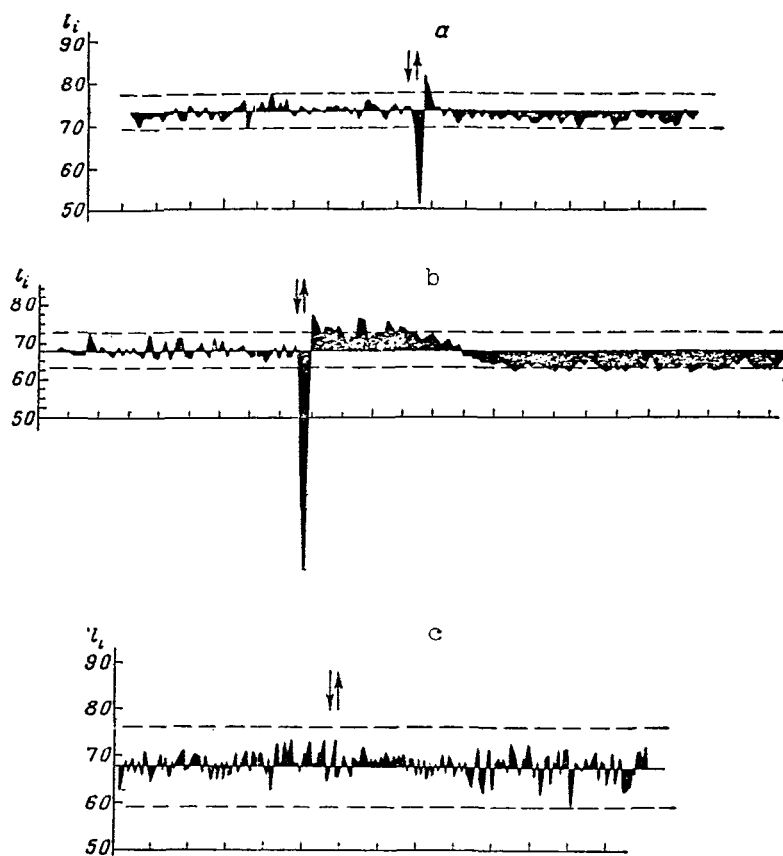


Figure 5. Area of thermogram deviations from mean resting level after second exposure of 30 sec on second (a), third (b) and seventh (c) days of experiment. Time mark 2.5 min. Arrows indicate time centrifuge was switched on and off.

The gradual intensification of the reaction after repeated exposures ($I < II < III < IV$) was characteristic. The negative change became less pronounced (V), but after the fifth startup of the centrifuge, when the interval between exposures was shortened to 5 min, it began to intensify once more ($V < VI < VII$). The reaction weakened slightly after the next startups of the machine. Prolonged exposures (60 sec) at the end of the experiment disrupted the process of stabilization and intensification again set in.

When the thermal cycle lasted 60 sec, i.e., one measurement of the blood flow produced an integral value for the entire period of centrifugation, there was a change in reaction from the total positive shift after the first exposure to the negative after the third and subsequent exposures, and the value of the negative shift systematically grew (fig. 7). On the next day of the experiment, the reaction was negative even after the first centrifugation and it continued to intensify after the following exposures. Following a day's interruption,

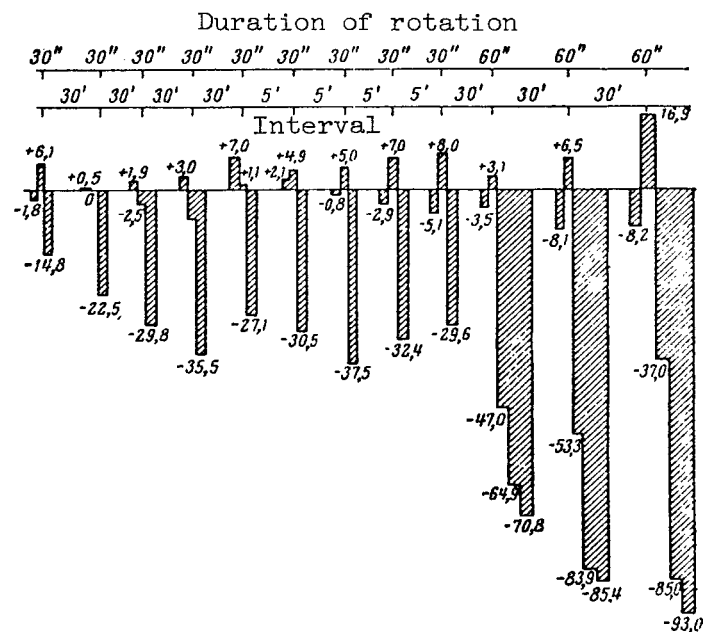


Figure 6. Deviations of individual l_i from mean resting level in percentages at time of exposure to several successive accelerations during single day of experiment.

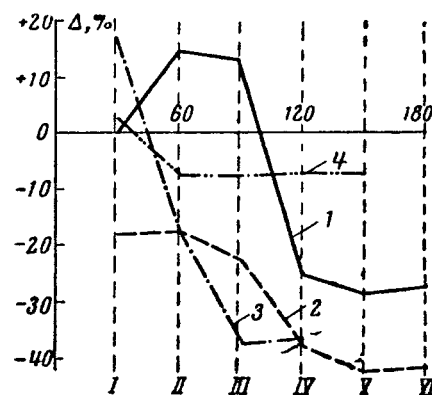


Figure 7. Deviations of values of l_i from mean resting level averaged for entire period of rotation in several successive exposures during four days of experiment. Curves 1, 2, 3, 4--days of rotation. Abscissa--time in minutes. Roman numerals--ordinal numbers of exposures during a single day.

the shift was again positive after the first startup of the centrifuge. Then the whole pattern was repeated. The order of the curves in figure 7 is as follows: first and second days of the experiment--without interruption; third day--after a day's interruption; fourth day--also after a day's interruption.

Figure 7 shows the intensification of the negative shift from day to day, except the fourth day of the experiment, when the negative shift became appreciably less. We observed a similar pattern in all 9 rabbits.

The reaction to centrifugation began to weaken after 2-4 days of the experiment. In two rabbits observed for 10 days, the intensity of changes in blood flow during centrifugation decreased at the end of this period and did not differ significantly from fluctuations in the blood flow level at rest (fig. 5c).

The initial stage of restoration was invariably represented by a distinct intensification of the venous flow (first phase of the aftereffect). ^{/43} From time to time this intensification was reflected in only one or two reduced thermal peaks, but even then the increased blood flow greatly exceeded the triple value of the root-mean-square for the background. In a few cases, several of the reduced thermal peaks were contained within the triple root-mean-square, but exceeded 2σ . The positive change in function was significant because it was present in every case and because of the "runs test" criterion. The intensity of this change was fairly well correlated with the value of the negative deviation in function from the mean value at rest at the time of the action. This relationship can be seen in figure 8. The data were obtained on the third day of an experiment with one of the rabbits.

Curve A represents a series of deviations in function, averaged for the entire time of rotation, from the mean resting level during successive exposures on one day of an experiment. The figures on the curves are the ^{/44} ordinal numbers of the exposure. Therefore, the points on the curves for the first (curve B) and second phases of the aftereffect (curve C) correspond to the analogous points on the first, second and succeeding experimental points on curve A. Figure 8 shows a qualitatively good negative correlation between the corresponding points on curves A (reaction during exposure) and B (reaction during the first phase of the aftereffect). This relationship between the reactions during rotation was observed in all 9 animals in the aftereffect.

Curve C in figure 8 reflects data for the second phase of the aftereffect, during which the venous flow decreased. The boundaries of the phases were established by the "runs test" criterion. The decrease in venous flow lasted 20-25 min. The extent of the negative change in function fluctuated throughout the second phase. The mean value of this change generally equalled the intensity of the preceding changes, but the qualitative correlation was not as good as for the first phase. In some instances, especially during the latter part of the experiment, the second phase was indistinct or absent. The dynamics of the phase changes in the aftereffect is shown in figure 5a-c, which presents the results of the exposures and subsequent fluctuations in level of the venous flow on the 2nd, 3rd and 7th days of the experiment.

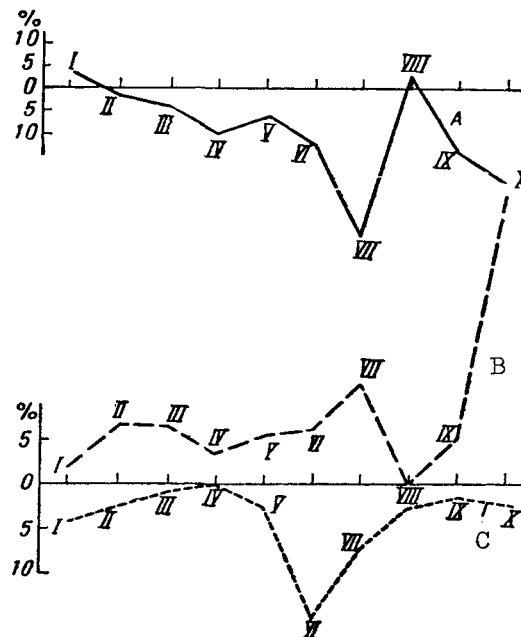


Figure 8. Mean deviations of l_i for period of rotation from resting level (in percent) following successive exposures on 1 day of experiment. A--centrifugation; B--1st phase of aftereffect; C--figures on curves--ordinal numbers of the exposures.

Besides providing data on blood flow changes, our method yielded information on the dynamics of changes in brain temperature near the place of the sensor. It was not our purpose to analyze these data in the present work. We wish merely to note that the brain temperature fluctuated around $37 \pm 2^\circ$. An intensification of the blood flow was accompanied by a rise in brain temperature, while a decrease in the blood flow coincided with a drop in temperature. The changes amounted to about 0.3° . Regardless of the blood flow, brain temperature fluctuations of the order of $0.3-0.5^\circ$ were very slow in developing--about 9 min were required.

In addition to these temperature changes, the site of the sensor was warmed at the time of the sharp decrease in blood flow during centrifugation due to the low transfer of heat by the moving blood.

Discussion

The marked decrease in venous flow after accelerations reaching a critical level or after prolonged exposures reflects the insufficiency of the cerebral blood supply that develops under these conditions. The fact that the rabbits died after exposures of more than 2 min confirms the probability that the cerebral blood supply seriously deteriorates during centrifugation. Evidence of

this is provided by the sharp drop in oxygen tension in cerebral tissues noted by Ye. A. Kovalenko et al. (1963) in centrifuged dogs. Some authors believe that oxygen tension, as measured in the brain by the polarographic method, ^{/45} is a direct indicator of the blood supply in the region under study (Cross and Silver, 1962).

The decrease in venous flow noted in our experiments occurred only at the end of 30 sec of rotation. Much of the 30 sec exposure came during the period of increased flow. In 2 out of the 9 animals rotated for 30 sec, we observed only an increase in the function under study. We assume that intensification of the flow reflects the mechanism of compensation. The 30 sec exposure to acceleration of 4-5 g in the head region was not really critical. However, repeated exposures over several days of the same animal did produce a virtually critical reaction. This phenomenon of "cumulation" is characteristic of the effect of acceleration, and it has also been noted in the course of flight training (Savin, 1957). Thus, there is exhaustion of compensation or summation.

It is fair to state, therefore, that the venous flow reaction to acceleration is not determined solely by the passive mechanical shifting of blood. It also includes the biological components of compensation. We also think it likely that there are trace reactions lasting at least a day to acceleration, which raises the question of whether neuroreflex mechanisms participate in these processes. The EEG changes that occur 2-3 hours after centrifugation of rabbits suggest that the answer is in the affirmative (Izosimov and Razumeyev, 1962).

The arteriovenous gradient of pressure and hydromechanical resistance of the cerebral vessels are the only factors that determine the level of the cerebral flow (Kety, 1949). After a sharp drop in arterial pressure "at the head level," the stability of the cerebral blood supply undoubtedly cannot be preserved without active vasodilatation, because the drop in venous pressure does not ensure an adequate arteriovenous gradient. An increase in venous flow and contraction of the venous system, as mentioned before, creates the physical conditions for effecting a decrease in resistance of the cerebral vascular system (possibility of increasing the size of the vascular bed of the arterial and capillary systems). After these possibilities of compensation become exhausted and insufficient, the general cerebral blood flow (and, therefore, the venous as well) decreases and the brain becomes anemic. If the doses are critical, death supervenes.

The two-phase fluctuations in the blood flow level observed in the after-effect are probably caused by change in CO₂ and O₂ concentrations in brain

tissues and in cerebral blood at the time of acceleration. It has already been mentioned that hypoxia (Kovalenko et al., 1963) and even hypercapnia may ^{/46} arise. The immediate effect is local automatic vasodilatation (Sokoloff, 1959).

Such, in our opinion, is the origin of the first phase of the aftereffect--intensification of the venous flow (here the general cerebral blood flow). The regularity with which this reaction occurs and its evident quantitative correlation with the extent of the negative shift at the time of centrifugation confirm our view.

The second phase of the aftereffect--decrease in cerebral blood flow--is less definite quantitatively. The long contraction of the venous flow during the second phase of the aftereffect is clearly indicative of diminution of the cerebral blood flow as a whole. This reaction can scarcely be regarded as the result of some preceding hypercompensation. The decrease in cerebral flow here is probably a reflection of the inhibited state of several systems, primarily the central nervous system. This has been observed in human subjects rotated on a centrifuge and in experimental animals (Kovalenko et al., 1963). In our experiments this stage of the aftereffect was indistinct or absent in well trained animals.

Study of the effect of acceleration on the venous flow proved to be a convenient model for observing the training process in animals. The rabbits became "well trained" after 3-4 days in the centrifuge. The days of rest helped them to become more tolerant of acceleration. However, exposures repeated over a number of days aggravated the injurious effects, as might be expected. It will be noted that the critical exposure for rabbits to the accelerations used in our work was close to that employed for similar exposures in a chest-back direction for man (Barer, 1962).

Conclusions

1. Acceleration in a head-pelvis direction initially intensifies and then slows the venous flow in the cerebral vessels of rabbits.
2. The venous flow reaction in the aftereffect is two-phase, consisting of a brief initial increase and then a prolonged decrease in blood flow.
3. Repeated exposures results in summation of the venous flow reactions.
4. Centrifugation over a number of days, including those free from acceleration, causes adaptation.
5. The venous flow reaction to acceleration in a head-pelvis direction is determined by the interaction of the passive mechanical factor with the factor of physiological compensation.

EFFECT OF PROLONGED ACCELERATION ON THE GROWTH OF THE ORGANISM
AND ON THE FUNCTIONING OF SEVERAL OF ITS SYSTEMS

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ABSTRACT

Rats attaining the age of 2-3 days were exposed to acceleration of 2-3 g 5-6 hours daily during 2-3 months.

The weight of experimental rats was smaller than that of the control. Special experiments showed that unfavorable conditions of food intake during rotation were not the single cause of the low weight of experimental animals. Motor activity in experimental rats during special test rotation was higher than in the control. Mortality under the action of lethal acceleration was the same in both groups. No difference between viability of experimental and control rats was observed.

In experimental rats the excitability of equilibrium organ was reduced. Bioelectric reaction of extremity muscles to adequate stimulation of vestibular apparatus was lower, the latency of reaction was longer and the duration of aftereffect was shorter. Bioelectric activity of skeletal muscles at rest in experimental rats was lower.

The latency of unconditioned defensive reflexes to a weak stimulus in experimental rats was longer than in the control; the latency of the reflex to medium and strong stimuli exhibited a tendency to shortening.

Investigation of the part played by gravitational forces in onto- and /48
phylogenesis and in the vital activity of organisms is of great theoretical and practical significance (Brovar, 1960; Isakov, 1963; Korzhuyev, 1963). It is helping to elucidate the role of gravitation as a factor in evolution, and is useful in predicting the effect of weightlessness during extended space flights and under the conditions of higher or lower gravitation (than on Earth) on small or large heavenly bodies.

Living organisms grown under conditions of prolonged rotation on a centrifuge are considerably different from the control. The effect of acceleration has been experimentally investigated in the following biological objects: micro-organisms (Montgomery et al., 1963) exposed to more than 100,000 g; bean and wheat seedlings (Edwards and Gray, 1956; Gray and Edwards, 1955)--10-500 g; *Drosophila* larvae (Wunder, Herrin and Crawford, 1959; Wunder, Crawford and Herrin, 1960)--1200-3000 g; turkey poults and chicks (Winget, Smith and Kelly, 1962)--1.5-6 g; mice (Wunder, Briney, Kral and Skaugstad, 1960); 1.5-14 g; rats and hamsters (Matthews, 1953; Briney and Wunder, 1962; Vrabiesku, Cimpeanu and Domilescu, 1963); turtles (Wunder, Lutherer and Dodge, 1963)--3-5 g.

After certain intensities of acceleration, there is generally some lag in growth and size of the experimental objects along with slight changes in body proportions. The relative weight of the heart and muscles of the diaphragm and femur increases, while in plants the stem diameter enlarges, i.e., the systems incurring the greatest functional load as a result of increased weight in ⁴⁹ the centrifuge. No signs of degenerative changes or susceptibility to disease or epizootic were noted in the experimental animals.

According to some authors, the cycle of vital processes is more rapid in these animals, with the consequence that their life span is shorter (Vrabiesku, Cimpeanu and Domilescu, 1963). However, the view that these characteristics (small size, short life span) are the result of specific adaptation to increased gravitation is overly simplified (Wunder, Lutherer and Dodge, 1963). Under certain conditions turtles, for example, are much bigger than the control. A factor of some significance is that the conditions in the centrifuge are unusual for the ingestion and digestion of food (Wunder, Lutherer and Dodge, 1963).

Functional tests and loads show that the experimental animals react somewhat differently from the control (Gyurdzhian et al., 1963). Besides the variety of influences exerted on the vegetative indices of developing organisms, some authors noted in similar investigations permanent changes in the animal sphere.

For example, extinction of the nystagmus reaction to repeated stimulation in chicks was less pronounced than in the control (Winget, Smith and Kelly, 1962). After rats were removed from the centrifuge, there was an unusual distribution of muscle tone, while decerebration resulted in exceptionally strong extensor tone (Matthews, 1953).

Our objective was to study the development and functional state of white laboratory rats grown under the conditions of prolonged daily exposure to centripetal accelerations. Two to 6 day old animals (half of the litter) were subjected to rotation on a special stand every day (except Sunday) for 2-3 months. The animals were kept in transparent plexiglas containers 250 x 250 x 250 mm in size. The maximum radius of rotation was 135 cm, maximum number of revolutions--30-40 per min, centripetal acceleration--about 2-3 g (fig. 1).

The other half of the litter served as the control. These rats were laid under another mother and not rotated. They were kept under more or less the same conditions as the control.

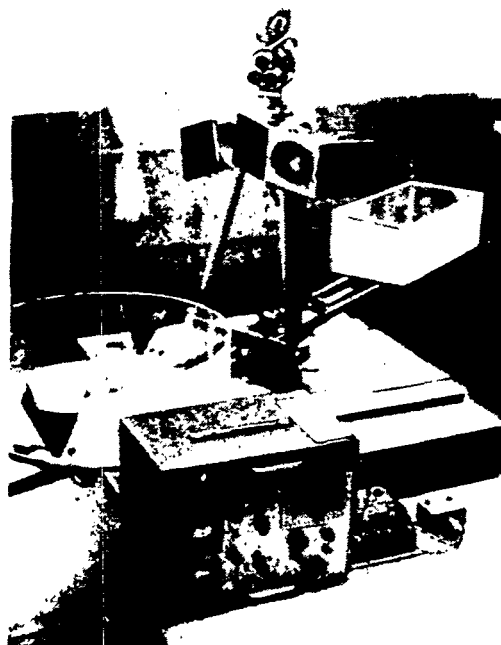


Figure 1. Rotating stand (general view).

The rats in the first series of experiments were rotated with their mother. While being rotated they were able to move about the box, suck the mother and take other food. In the second series, the animals were rotated without the mother. At the time of rotation the control rats were also removed from the mother. We were thus able to eliminate the probable harmful effect of acceleration on the intake of food and early stage of digestion. /50

Some 71 control and 85 experimental rats (17 litters) were used in the investigation, which included the following:

(1) general observation of the condition, behavior, and development of the young animals and regular weighing;

(2) hematological analysis;

(3) investigation of background electric activity and electromyographic reaction of muscles in the hind leg to adequate stimulation of the vestibular apparatus (rocking);

(4) investigation of the threshold of excitability and length of the latent period of the unconditioned protective motor reaction.

Observation of the general condition and behavior of the animals failed to reveal any significant differences between the experimental and control rats.

Natural death from various causes was also about the same in both groups. Although the animals were able to move about during rotation, they spent most of the time as far away from the center of rotation as possible, with the result that the centrifugal force and gravity were directed along the back-chest axis of the body.

The behavior, motor activity and coordinating movements of the animals were filmed in a special large box on the rotating stand during accelerations of about 5 g and immediately after the action was halted. The experimental ^{/51} rats proved to be much more active than the control. At medium intensities they moved about, clambered up the sides of the container and showed well coordinated movements. As soon as the rotation stopped, they resumed their normal motor activity. On the other hand, the control rats sat curled up while being rotated. After the action was halted, they remained motionless for a long time and their fur was disheveled. The experimental rats defecated and urinated frequently, whereas the control animals were much cleaner. It is our impression that urination and defecation were inhibited in the experimental animals during rotation, but these acts were quite free in the controls.

Sixteen experimental and 16 control rats were exposed to accelerations of about LD₅₀ (20-25 g, 5 min) in a laboratory centrifuge (36 cm radius). However, there was no significant difference in mortality rate between the two groups.

The dynamics of the relative weight of the experimental animals in percentages of the weight of the controls is shown in figures 2 and 3. Figure 2 presents the results of the first series of experiments on 59 experimental and 45 control animals (10 litters) which remained with their mothers and were able to take nourishment during rotation. Forty-three of them were exposed to 1.5-2 g (curve 1), 16-0.8 g (curve 2), because they were in the container situated closer to the center of rotation of the stand.

The experimental animals gained weight more slowly than did the control ^{/52} from the very first days of rotation. At low intensities of acceleration (0.8 g), the lag in weight was less pronounced than at the higher intensities (1.5-2 g).

The curves were undulant. For example, the experimental animals gained weight quite slowly during the first days of rotation, but by the 10th day they did so somewhat more rapidly, and by the 50th day they weighed almost the same as the controls. Unfortunately, the daily rotation of the animals was halted at this time (50-60 days from birth). It is therefore difficult to say what the final segment of the curves would have been like had the daily sessions continued. Our material is too meager for a statistically significant evaluation of the individual waves on the curve, i.e., the phases (periods) of larger or smaller lag in weight of the experimental animals. Only the general nature of the curve is beyond question, i.e., the weight of the experimental animals was less than that of the controls as long as they were exposed to daily accelerations. The higher intensities of the action made them lag even more behind the controls than did the lower intensities.

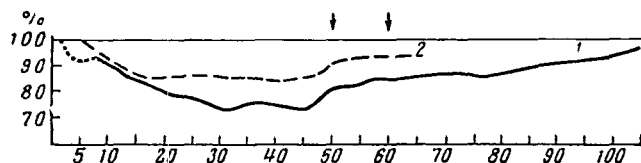


Figure 2. Dynamics of average weight of experimental rats in percentages of weight of controls (general nature of curves is shown).

1--experiments with accelerations of 2-3 g. First part of curve, broken lines, is hypothetical because of insufficient data to determine statistical significance;
2--experiments with accelerations of 0.85 g. Arrows show age of rats (50-62 days) when daily rotation was halted. Abscissa--age of animals in days--percent of weight of control animals.

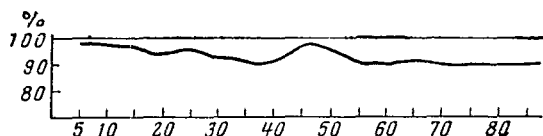


Figure 3. Dynamics of average weight of experimental rats in percentages of weight of controls (general nature of curves).

Abscissa and ordinate--same as in figure 2.

Figure 3 reflects the results of the second series of experiments performed on 26 experimental and 26 control rats (7 litters), which were removed from their mothers in the rotation period and received no food. The curve of the relative weight of the experimental animals is much higher than that in figure 2. However, here too they clearly lagged behind the controls.

Like figure 2, figure 3 shows the undulant quality of the curve. However, further study will be needed to elucidate the elements involved in the weight changes of the rats grown under the conditions of prolonged exposure to acceleration and the underlying physiological mechanisms. The one thing that is clear is that the unusual circumstances connected with feeding during accelerations play a definite if not exclusive role in the slow growth and weight gain of the experimental animals.

Combined biochemical investigations of the blood and urine throw some light on the mechanisms of influence of prolonged acceleration which may be manifested in adaptive or degenerative changes. The investigations of the blood and urine provide information about the metabolic processes in general, protein and nucleic metabolism in particular (Gyurdzhian et al., 1963; Baranov et al., 1963). Our own investigations will be discussed in a special report.

These data indicate that gravitational conditions, specifically acceleration, influence in one way or another (the alimentary factor is not inconsiderable) the morphogenesis and state of the autonomic functions of the animal organism.

In addition to the effect of gravitation on the autonomic indices of the experimental animals, we were also interested in the state of their animal sphere. Accordingly, we studied vestibular function and the unconditioned defense reflex in 17 experimental and 17 control rats from both series of experiments, fed during rotation and at other times. The results of both series of experiments were in principle the same. The electromyographic reaction of the animals' hind leg served as the index of the physiological state of the vestibular apparatus. Graduated rocking around the longitudinal axis of the body was used for adequate stimulation of the receptors of the vestibule. The rocking was carried out on a special piece of equipment for 10 sec at a frequency of 0.6 cycle per sec and with a maximum angle of slope of 25° .

In each test the electromyogram was recorded 3 times for 10 sec: before, during, and after vestibular stimulation. The EMG data were processed simultaneously with the tracing (an integrator was used for this purpose). They were recorded in the form of relative values from the readings of a mechanical counter. The resultant data were statistically processed by Student's method.

The electromyograms of the control animals were uniform oscillations of potential with an amplitude of 10-40 μv . When the animal was rocked, the EMG showed periods of increased electric activity reaching 80-250 μv .

The aftereffect of the reaction to vestibular stimulation was manifested either in 3 or 4 periods of increased electric activity or in a general uniform increase in amplitude of the muscle currents (to 60-120 μv). The average duration of the aftereffect was 0.4-2 sec. The length of the latent period of the electromyographic reaction to rocking fluctuated between 0.07 and 0.3 sec.

Investigation of the experimental rats showed that their general level of muscle bioelectric activity both at rest and during the vestibular-tonic reaction to rocking was much lower than in the control animals. /54

The background muscle electric activity (the animal sat quietly in the chamber) of the experimental rats was less than half that of the controls. The EMG leveled out, impulses were rare and their amplitude dropped to 5-20 μv , sometimes even to the noise level (figs. 4a and 5). These EMG changes were statistically significant ($P < 0.02$).

During vestibular stimulation (rocking of the animals) the absolute level of bioelectric activity in the group of muscles under study was about 2.5 times less in the experimental animals (fig. 4b) than in the controls ($P < 0.01$). However, we cannot safely conclude from this that the EMG reaction to rocking was weaker because their background electric activity was less. The difference in ratio of electric activity during vestibular stimulation to background activity as between the two groups of animals was statistically insignificant ($P < 0.056$), although it tended to be less in the experimental animals than in the controls.

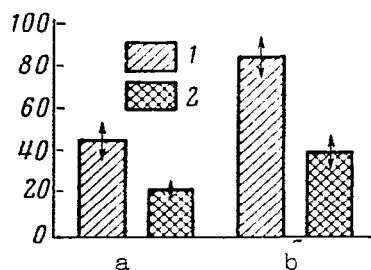


Figure 4. Electric activity of muscles at rest (a) and in response to adequate stimulation of organ of equilibrium (b)--vestibular- tonic reflex. 1--control; 2--experiment. Ordinate--integral muscle bioelectric activity in relative units.

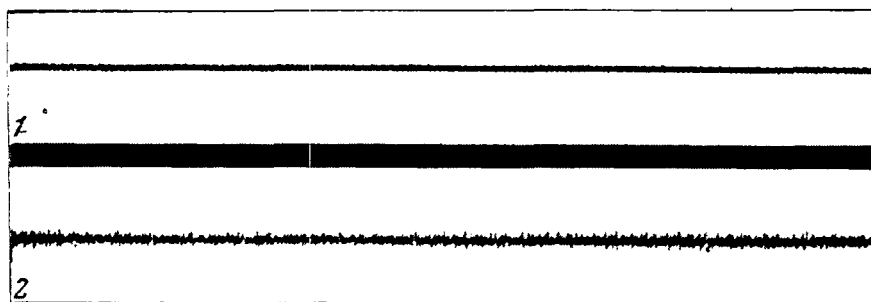


Figure 5. Electromyograms of muscles in hind leg of animals at relative rest. 1--experiment; 2--control.

The latent period of the vestibular- tonic reaction of the experimental animals was much more significant ($P < 0.005$) than in the controls (fig. 6a). The average duration of the latent period was 0.18 and 0.5 sec for the experimental and control rats, respectively. In 2 rats, however, it was so long that it could scarcely be determined, because the reaction was not manifested until the second or even third rocking.

Weakening of the reaction to stimulation of the vestibular organ was reflected in the experimental rats not only in a lengthening of the latent period, but in a marked shortening of the duration of the aftereffect (fig. 6b). The aftereffect of vestibular stimulation (rocking) averaged 1 and 0.24 sec ($P < 0.02$) in the control and experimental animals, respectively. Frequently the latter had no aftereffect at all. Their muscle bioelectric activity in the aftereffect period, like the previously noted electric activity before and during vestibular stimulation, was almost half that of the controls ($P < 0.03$).

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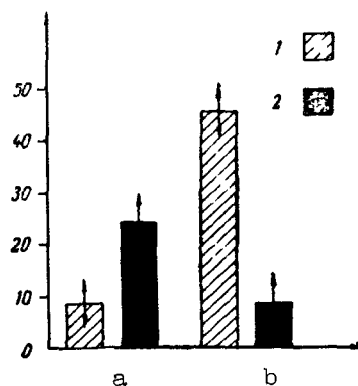


Figure 6. Duration of latent period (a) and aftereffect (b) of vestibular-tonic reflex of experimental and control rats in relative units.
1--control; 2--experiment.

Thus, in rats grown under conditions of prolonged daily exposure to acceleration in a centrifuge, the vestibular-tonic reaction has important characteristics. Electromyographic activity when they were resting was much lower, and their reaction to vestibular stimulation was appreciably weaker than in the controls. Consequently, prolonged daily acceleration influences the growing organism and the functioning of the vestibular analyzer.

Investigation of the unconditioned motor reflex, i.e., functional state of elements of the unconditioned spinal reflex arc, was deemed of great value in analyzing the coordination of movements and postural-tonic reflexes of the experimental animals. The threshold of excitability and latent period of the defense motor reaction to pain were selected as indices of the functional state of the spinal reflex arc. The latent period was recorded accurate to 0.5 msec by the method described in M. A. Kuznetsova's article (elsewhere in this collection), in order to determine the effect of acute whole-body gamma irradiation. Painful electric stimulation was effected by plastic electrodes placed on the front and hind paws of the animal. /56

Electric stimulation was provided by an alternating current from a sound generator with a frequency of 100 cps and duration of 0.03 sec. Three physiological intensities of the current were used--weak, medium, and strong--equivalent to 3-, 6-, and 10-fold threshold values. To ensure physiologically constant intensities of stimulation, the experiment was designed in such a manner that the determination of the latent period of the reaction to the stimulus of a given intensity was invariably preceded by the determination of the threshold. Accordingly, the following indices were determined in this order:

- (1) threshold;
- (2) latent period of the reflex to the weak stimulus (3 measurements);

(3) threshold;

(4) latent period of the reflex to the reflex of medium intensity (3 measurements);

(5) threshold;

/57

(6) latent period of the reflex to the strong stimulus (2 measurements).

The results of investigating the defense motor reflex showed that the experimental rats did not differ from the controls in thresholds of excitability.

But the situation was different as far as the duration of the latent period was concerned. There was a slight difference between the two groups in length of this period (figs. 7, 8 and 9). Although processing the data by Student's method and by the χ -square criterion failed to confirm the significance of the differences, yet the trend of the changes was regular. The latent period of the reaction to the weak stimulus was perceptibly longer in the experimental rats than in the controls (fig. 7). However, in the reactions to medium and strong stimuli, the experimental animals tended to have a shorter latent period than did the controls (figs. 8 and 9).

It will be noted that in the rats used in the second series of experiments, when the animals received no food while being rotated, these changes in the latent period in response to the medium and strong stimuli were less pronounced among the experimental animals than they were in the first series. We are inclined to ascribe this to the fact that during the first series the rats were exposed to daily rotation longer (3 months) than during the first series (2 months).

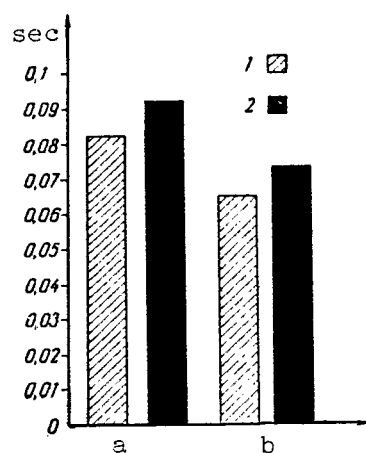


Figure 7. Duration of latent period of unconditioned defense reaction to weak stimulus.
a--first series of experiments; b--second series;
1--control; 2--experiment.

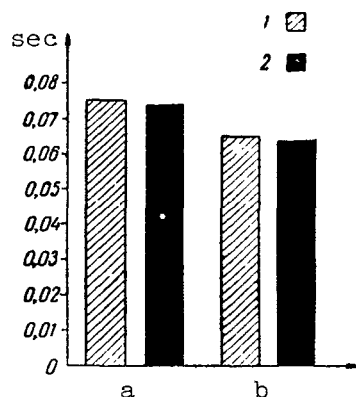


Figure 8. Duration of latent period of unconditioned defense reaction to stimulus of medium intensity. Symbols same as in figure 7.

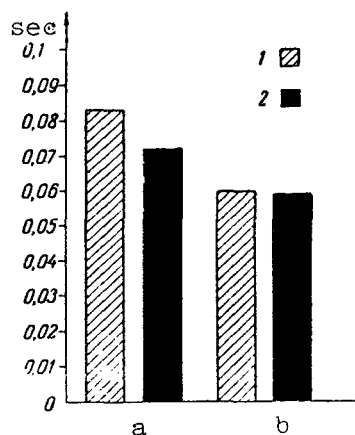


Figure 9. Duration of latent period of unconditioned defense reaction to strong stimulus. Symbols same as in figure 7.

Thus, the unconditioned defense reaction in the experimental rats was characterized by slight lengthening of the latent period of the reaction to the weak stimulus and a tendency for it to become shorter in response to the medium and strong stimuli.

This response of the nervous system is presumably rational and adequate, because it is in harmony with the well-known law of force in the physiology of higher nervous activity. An animal reacts slowly to a weak, though important, stimulus, and it reacts quickly to a significant and strong stimulus.

The decrease in electric activity of the muscles, lengthening of the latent period and shortening of the aftereffect of the reaction to adequate vestibular stimulation (i.e., decrease in excitability of the vestibular-tonic reflex) in experimental animals grown under the conditions of a heightened background of vestibular stimulation (prolonged daily rotation) can in all probability also be regarded as a suitable adaptive reaction of reorganization of the nervous system. A comparison of the results of the vestibular-tonic and motor defense reflexes shows that both have an efferent component in common. /58

Study of the autonomic indices and weight dynamics reveals that growing rats under conditions involving prolonged exposure to acceleration has a marked effect on their morphogenesis and reactivity. The experimental animals, according to our data, gained weight much more slowly than did the controls, the degree of lag being proportional to the intensity of the action.

A single exposure to 10 g for 5 min elicited a reaction of increased concentration of nonesterified fatty acids in the experimental animals which differed from that of the controls. In the former the reaction was slow and it set in later (Gyurdzhian et al., 1963).

The alimentary factor (difficulties in taking and assimilating food while being rotated) played some part in the process. However, it was far from being the only cause, because a similar pattern, although not as pronounced, was also observed in the second series of experiments in which neither the experimental animals nor the controls received food while being rotated.

We do not have the information to permit us to judge whether the changes noted in the experimental rats were adaptive or degenerative in nature. For one thing, they continued to be just as viable as the controls, a fact that militates against the idea of degenerative reorganization in the experimental animals.

However, they were more active than the controls both during and immediately after rotation in a large container (acceleration up to 5 g). But this fact cannot be regarded as evidence of adaptive reorganization since the unexpected new stimulus probably acted on the control rats as a form of external inhibition (movements, defecation and urination were inhibited).

The mortality rate from brief exposure to lethal accelerations (20-25 g, 5 min), as mentioned before, was the same in both groups of animals. This is not surprising since the rats were exposed to weak accelerations (2-3 g). But the reaction to these accelerations was qualitatively different from the mechanism of action of lethal accelerations (20-25 g). /59

Conclusions

1. Growing rats under the conditions of prolonged (5-6 hours) daily exposure to accelerations (2-3 g) affects the development of the animals.

2. The influence of gravitational conditions is reflected both on the vegetative sphere (weight dynamics, intake and assimilation of food, hematopoiesis, etc.) and on the animal sphere (electric activity of muscles, vestibular- tonic and unconditioned defense reflexes).

3. It is reasonable to assume from the nature of the vestibular-tonic and unconditioned defense reflexes of experimental rats exposed to acceleration that adaptive reconstruction develops in the animal sphere, which is adequate for the environmental conditions.

We express our thanks to N. N. Livshits, O. G. Gazenko, and P. V. Vasil'yev for their valuable advice and help in this work.

EFFECT OF VIBRATION ON THE NERVOUS SYSTEM

L. D. Luk'yanova

ABSTRACT

Based on the literature and personal investigations, the author shows the effect of local and total, single and chronic vibration on the state of the peripheral and central nervous systems. The problem of the mechanism of vibration effect on the living body is considered. A generalizing scheme of vibration influence on the nervous system is suggested. This scheme reveals the possibility of formation of the regions of steady excitation in the spinal cord and the higher parts of the central nervous system.

Vibration is one of those external agents whose effects are closely intertwined with those resulting from extero-, proprio-, and interoceptor stimulation. Prolonged contact with the sources of vibration is known to give rise to the serious disorder called vibration disease. /60

Vibration has a powerful effect on animals and human beings, whether they are exposed to it briefly or over a long period of time. Now that human beings are exposed to it in industry and during space flight, preservation of the efficiency of the various divisions of the central nervous system is a matter of primary importance. Therefore, a thorough study of the reactions arising as aftereffects of vibration and the effect of these factors on the CNS is essential.

The physical parameters of vibration are frequency, amplitude, rate and acceleration. The principal etiological factor in vibration disease, according to most investigators, is frequency. However, vibrations with a low frequency (less than 16 cps) are usually characterized by acceleration. Herein is manifested the specific reaction of the vestibular apparatus and mechanical displacement of the viscera, which stimulate numerous receptors.

Vibrations are now tentatively divided into two frequency ranges: up to 16-20 cps and from 16-20 to 250 cps or more. The following composite table is from the work of Ye. Ts. Andreyeva-Galanina and V. G. Artamonova (1963), and it gives an idea of the effect of various frequency spectra of mechanical vibrations on the body.

Frequency of vibrations, cps	Nature of effect
Region of infrasonic frequencies:	
up to 15	Acts by acceleration. Causes displacement of the body organs and reaction of vestibular apparatus.
up to 25	Still perceived as separate impulses. Bone and joint changes.
up to 35	Discrimination of tonality; individual symptoms of vibration disease appear, spasm still rare.
Region of sonic frequencies:	
50	Vibration disease with angiospasm.
250	Limit of vasospasm formation, possibility of vibration disease apparently excluded.
Region of ultrasonic frequencies:	
16,000 and higher	Conversion of mechanical energy into thermal; bactericidal effect, cavitation, effect on CNS, etc.

This division is based on the principal symptom of the disease--neurovascular spasm, which is characteristic of the second or sonic group of frequencies (Guillemin and Wecksberg, 1953). However, within this region the effect of vibration of different parameters also varies. For example, most cases of vasospasm arise, according to Ye. Ts. Andreyeva-Galanina, at a frequency of 100 cps. On either side of this frequency spasms are rarer. The optimum conditions for the development of other disturbances seem to vary from case to case. For example, after recording the electric activity of the brain and muscles, several authors showed that the effect of stimulation increases, achieving a maximum at a frequency of 50 cps (Terent'yev, 1958; Donskaya and Stoma, 1960; Rumyantsev, 1960; Volkov et al., 1960). The effect is somewhat less in the 90-100 cps range (Rumyantsev, 1960), whereas with frequencies of 250-300 cps changes in the above parameters are indistinct. Data on the effect of vibration with frequencies above 250-300 cps are somewhat contradictory, apparently because studies on the subject have been few in number. Nevertheless, these frequencies are believed to cause vasospasm, although not too pronounced (Malinskaya, 1962; others).

Considerable significance has been attached of late to the physical characteristics of the amplitude. Intensification of the response is generally proportional to the increase in amplitude of the vibration. It will be noted that the development of a pathological process depends not only on the frequency and amplitude characteristics of the vibration, but on its duration. Brief exposure to vibration does not, as a rule, cause irreversible changes. The present-day forms of vibration disease result from chronic contact with the irritant over a period of several months or even years. The site and area of exposure are also significant in the origin of the disease. It is now possible to differentiate between "local" and "general" vibration.

Involvement of the vascular system was at first regarded as the dominant symptom of the disease (Aronovich, 1926; Kryshova, 1929; Antonovskiy and Krichevskiy, 1929; Kostyukova, 1932; Telford, McCanne and McCormack, 1945). Hence the name of the disease for a long time reflected the nature of the vascular disorders (analogs are Raynaud's disease, "vasospastic disease of the hands due to trauma," etc.).

However, fuller descriptions include among the symptoms, besides changes in vascular tone, impairment of sensitivity, trophism, secretion, etc. (Vaynshteyn, 1937). Impairment of the autonomic functions is more than local, for it affects several organs and systems (Gratsianskaya, 1947; Drogichina and Kozlov, 1957; Sozon-Yaroshevich;¹ Shamardina, 1959).

In most cases, these symptoms are apparently due not only to the direct mechanical effect of receptor stimulation, but to reflexes.

For example, even though a limited portion of the body is exposed to vibration, the effect on vascular tone is generalized (Shamardina, 1959; Abramovich-Polyakov, 1962). Loecle (1950) found that the popliteal tendon reflex was inhibited by exposure of the inguinal vascular nodes to vibration. Similar action on the femoral artery also completely inhibited the reflex, but action on the artery separated from the nerves did not have this effect.

The effects on pain sensitivity are also diffuse, for they may embrace the entire surface of the fingers, hands and forearm. Symptoms of the pronounced form of vibration sickness also include disorders of the segmental type--segments C₂ - D₈ (clinical data; Artamonova, 1963). /63

Reflex changes arising in gastric and intestinal function after exposure to vibration were described by V. P. Ryumin (1950) and V. G. Artamonova (1960). Pathological changes in the stomach involve impairment of motility and secretion, sometimes associated with mucosal changes.

These and a host of other changes, the list of which is extensive, take place against a background of marked functional disorders. The earliest investigators of the local action of vibration noted the development of sleepiness,

¹Cited from Ye. Ts. Andreyeva-Galanina, 1956.

which continued even after the action was halted (Chigayev, 1894; Borishpol'skiy, 1898). Subjecting the head of animals to 10-15 min of vibration, Borishpol'skiy found decreased excitability of the cortex and nerve trunks and changes in blood circulation, especially pronounced after 5-6 sessions.

Later investigators encountered the phenomenon of inhibition in the cerebral cortex (Breytman, 1908; Nauman, 1914; Kerman, 1940; Lebedeva, 1953). Lebedeva was able to show that the sleep of rats exposed to vibration for several hours was so deep, that the animals could be transferred to another chamber without waking them.

A. Ye. Shcherbak (1903), exposing the knee-joint region of rabbits to vibration, observed an increase in the patellar reflex, functional clonus of the knee when tapped and in passive movement and foot clonus. The length of the latent period was shortened. Following prolonged vibration, spastic tremor lasted 20 days, with an increase in the patellar reflex persisting even after a month.

Vibrations applied to the ends of the femur with artificial fracture caused clonus in the intact leg and led Shcherbak to conclude that the phenomenon was of central origin.

Local vibration applied in the region of the foot and shin intensified the deep reflexes. Repeated vibration strengthened, while a single and brief exposure weakened and even destroyed them.

O. L. Ledeneva (1936) observed a similar increase in reflexes after repeated vibration of the symphyseal region.

In later studies (1907-1908) Shcherbak showed that the patellar reflexes sometimes do not appear after vibration in the joint region in the presence of even high excitability, apparently because of the developing inhibition induced by extreme stimulation. Along with an increase in the deep reflexes, Shcherbak observed a persistent decrease in the skin reflexes, sometimes to the point of complete disappearance. /64

The application of brief local vibration (once every 3 hours or for an hour daily) to the paw of rabbits had the following effect. Simple contact with the end of the foot after several sessions of vibration caused foot clonus in either the touched or untouched leg or in both (Minetskiy, 1960).

Study of the latent period of the conditioned motor reflex in patients with vibration disease revealed the existence of severe functional disorders with excitation predominating. G. I. Zuyev (1960) and D. A. Ginzburg and A. B. Cheremnykh (1961) found a decrease in the alpha index, sometimes no alpha activity in the recording, and predominance of low-amplitude beta rhythms in all leads. The EEG changes were chiefly functional in character.

Ye. Ts. Andreyeva-Galanina (1956) refers to A. Ya. Sozon-Yaroshevich, who conjectured that stagnant foci of excitation (parabiosis) and protective

inhibition of the "vibration centers" of the brain arise in the spinal cord under the influence of vibration.

D. K. Abramovich-Polyakov (1962) provided clinical confirmation of the state of parabiosis in the centers regulating arterial pressure and vascular tone in vibration disease. However, the spastic reaction of the blood vessels is caused by parabiosis in both the peripheral and central nervous systems. The development of a parabiogenic focus in the lateral horns of the spinal cord, according to Sozon-Yaroshevich (1956), also accounts for the degenerative changes noted in the bones of the extremities.

Investigation of the functional state of the neuromuscular apparatus of persons suffering from vibration disease revealed increased excitability, change in lability and development of parabiosis (Drogichina, 1961).

The development of muscular atrophy and contractures are attributed by many authors to the formation of stagnant foci of excitation in the spinal cord centers under the influence of a constant inflow of impulses from injured sensory nerves (Butkovskaya, 1957; Pavlova, 1958; Vozhzhova and Lebedeva, 1960; Malinskaya, 1962; Artamonova and Stoma, 1963).

It follows from the foregoing that local vibration may cause a severe systemic disease against a background of functional disorders of the central nervous system.

The earliest symptoms of a pathological process are increased excitability in the afferent part of the reflex arc and paranecrosis in the periphery. As the disease progresses, the second and third phases of parabiosis take place in the peripheral links and centers with no signs of ascending nerve injury or local degeneration.

However, irreversible changes are quite rare, and then only after prolonged (several years) contact with vibration.

"General" vibration has a much more powerful effect on the central nervous system. Pathological changes may develop even after a single exposure.

For example, N. I. Galat (1958, 1960) found that unconditioned reflexes were inhibited in patients, as shown by a lengthening of the time of reflex development of muscular contraction and decrease in intensity of the reflexes during 3-40 min of general vibration. These phenomena were intensified as the length of exposure was increased. The reflexes were restored 15-20 min after vibration was halted. The author ascribes these changes to a lowering of CNS excitability on the assumption that the irradiated inhibitory process may originate there. It is interesting to note that repeated fractional vibration produced fewer changes than did single prolonged vibration. This phenomenon is apparently due to activation of the restorative processes in the intervals between stimulation, which prevent the nerve cells from becoming exhausted.

M. A. Kuznetsova (compare her article in this collection) found that vibration stimulated the development of parabiogenic phases in the functional state of

the reflex arc of the passive defense motor reflex. These phases were similar to those which appear in the higher divisions of the CNS in experimental neuroses and under the influence of various physical and chemical agents.

Similar results were obtained by V. G. Terent'yev (1958). Using vibration with a frequency of 10-70 cps, he also observed the onset of general inhibition in direct relation to the physical parameters of the vibration. The latter weakened cortical activity and gave rise to phasic states and diffuse protective inhibition, impairing meanwhile cortical-subcortical relations. The activity of the subcortical centers was either intensified or weakened (disappearance of unconditioned vascular reflexes). Sometimes it was unbalanced. Caffeine restored normal cortical activity and cortical-subcortical relations. In view of the exciting effect of this agent on the cerebral cortex, the ¹⁶⁶ author assumes that the cerebral cortex here plays a regulatory role in execution of the reflexes to vibration. The functional state of the spinal cord changed (e.g., decrease in tendon reflexes of the extremities).

The EEG picture after strong vibration confirmed the presence of inhibition in the CNS.

Using approximately the same parameters (frequency of vibration 25 and 50 cps, time of stimulation 2-4 hours), S. I. Karchmazh (1962) found that the latent period of the conditioned motor-food reflex in rats increased, until the reflex disappeared entirely. There were no transitional phasic states (differentiations persisted as did the relationship between the vibration parameters and intensity of the animal's response). All this suggests disruption of the balance between the main cortical processes of excitation and inhibition after exposure to a strong stimulus resulting in fatigue of the cortical cells and development of protective inhibition. According to the author, the onset of this process and its disappearance after the halting of vibration take place quickly.

The effect of vibration on conditioned activity, as shown by the investigation of N. N. Livshits (compare his article in this collection) was more distinct (frequency of vibration 70 cps, time of stimulation 15 min). There was an immediate loss of reflexes and appearance of paradoxical phases. This state of protective inhibition persisted for several days and, in some animals, even intensified.

Functional impairment of the CNS was observed in a study of the interaction of various analyzers (Butkovskaya, 1957; Andreyeva-Galanina and Butkovskaya, 1960). General vibration of 30 and 50 cps weakened the interaction of the olfactory and vestibular apparatuses and sometimes completely distorted the reaction.

Highly interesting data were obtained in an investigation of brain bioelectric activity in man during and after vibration (Volkov et al., 1960). One-hour vibration with a frequency of 50 cps gave rise to exaltation of the alpha rhythm in the temporal cortex, followed by depression in the temporo-occipital and temporofrontal regions. In some instances the reaction was in the reverse direction. All this suggests the presence of a parabiogenic phase. At times signs of overexcitation were discernible. Thus, cortical bioelectric

activity following this kind of vibration is indicative of gradual, deep in-/67hibition involving the subcortex as well. The latter is manifested in a blocking of the vestibular-autonomic reflexes, a phenomenon responsible for the scarcity of functional changes in the cardiovascular system, drop in pulse pressure, and alteration of vestibular chronaxie with a tendency toward distortion of the intensity relations.

A cortical block by chloral hydrate after a shortening of vestibular chronaxie resulted in disinhibition of the vestibular-autonomic reflexes and more drastic changes in the cardiovascular system. The authors mention the significant fact that the altered EEG showed signs that some of the cortical zones were depressed (auditory region--lowering of the threshold of hearing) and that other regions (motor) were characterized by stagnant phenomena.

L. D. Luk'yanova, after studying changes in oxygen consumption by brain tissue during and after vibration, came to a similar conclusion. She ascribed the three successive phases (increased oxygen consumption, decreased oxygen consumption and restoration period) to a focus of protective inhibition arising in the higher divisions of the brain as a result of overexcitation of the nerve cells. As in her earlier work, she observed that vibration has a variable effect on different divisions of the brain.

Thus, most of the authors who investigated the effect of brief vibration on the nervous system favor the view that a focus of protective inhibition develops in the brain following overexcitation of the nerve cells.

The effect of vibration on the systems responsible for adjusting body position and movements is assigned a special role in the development of a pathological state in the higher divisions of the brain.

G. I. Rumyantsev (1960) observed the formation of stagnant foci of excitation with their tendency to concentrate in the motor and acoustic zones, along with increased excitability of the vestibular nerve. I. Ya. Borshchevskiy et al. (1958) and V. R. Usenko (1961) stress the increase in reactivity of the vestibular apparatus. E. A. Drogichina and N. B. Metlina (1962), V. R. Usenko (1961), and Ya. S. Temkin and P. S. Kublanova (1960) note the occurrence of vestibular disorders as a result of vibration, e.g., vertigo, reduced excitability of the labyrinth, total or partial loss of the rapid component of nystagmus, disharmonic reactive movements, etc. The authors relate these phenomena not so much to disturbances in the peripheral labyrinth as to changes in the central pathways of the vestibular nerve and its connections with other nerves. In most cases the disorders are associated with other lesions of /68the central nervous system, although they are often the initial symptoms of vibration disease.

References to the fact that vibration of certain parameters acts on the organism chiefly through the vestibular apparatus may be found in the studies of V. P. Zagryadskiy (1957) and M. R. Mogendovich (1961). And, finally, Z. I. Apanasenko (compare his article in this collection) showed that vibration may give rise to functional changes localized in the vestibular and motor analyzers. In the former, changes occur in the latent period and duration of the after-effect of the vestibular-tonic reaction; in the latter, changes occur in

spontaneous bioelectric activity while at relative rest. These changes reflect fairly persistent excitation, a process sustained in these systems for several days after exposure.

The phenomena that arise after one or more exposures to general excitation are cumulative and result in an extremely severe progressive disease of the central nervous system, the cerebral form of vibration disease. The main symptoms of this disease are localized vascular disturbances in the basal portions of the brain and its meninges (the earliest changes), functional neurodynamic disturbances of cortical-subcortical activity, signs of involvement of the diencephalon, tiny scattered focal symptoms (angiospasm of the small blood vessels, etc.), autonomic polyneuritis, and degenerative changes in the skeletal bones (Mel'kumova, 1960). The unfolding of the clinical picture of the disease is paralleled by changes in higher nervous activity reflected in the following (Andrianov, 1960; Borshchevskiy et al., 1958a, 1958b; Butkovskaya and Koryukayev, 1963; Rumyantsev, 1960; Zuyev, 1960):

(1) change in the correct correlation of intensity and mobility of the principal nerve processes, pathological sluggishness of the stimulatory process upon reduction of the force of the inhibitory process (active inhibition);

(2) development of phasic states;

(3) impairment of induction relations between the cortex and subjacent divisions of the brain, weakening of cortical activity upon disinhibition of the subcortex;

(4) disruption of the interaction of the signaling systems.

The process is clearly organic and reversible only in the earliest stages. It is later associated with focal cerebral microsymptoms. It follows a severe course and does not respond to therapy. That is why these disorders of ¹⁶⁹ higher nervous activity cannot be regarded as a manifestation of a neurosis in the Pavlovian sense of the term. A decrease in the intensity of active internal inhibition in the cortex is the first disturbance associated with the initial stage of the clinical picture. This process is the youngest phylogenetically and is, therefore, quite brittle. The subcortex becomes disinhibited, owing to the loss of tone by the most reactive portion of the central nervous system (cerebral cortex). Only then is the intensity of the excitatory process affected (second stage). Deep pathophysiological changes take place in the higher divisions of the central nervous system at the height of the disease--psychosensory disorders in the form of visual and auditory hallucinations. However, it is not a mental disease (third stage).

Electrophysiological investigations of patients with vibration disease also reveal that three nonspecific but characteristic EEG changes take place in succession (Shpil'berg and Mel'kumova, 1960). The first stage is marked by synchronization of the alpha rhythm, a sign of parabiogenic influence of the subcortical formations on the weakened cerebral cortex. A more severe clinical picture is associated with the development of slow waves (second stage). Finally, there is an unstable but increasingly persistent desynchronization of

the rhythms, which indicates a weakening of the synchronizing mechanism of the brainstem reticular system and permanent focus of excitation in the cerebral cortex (third stage).

The original state of the central nervous system as well as the individual characteristics of the organism and type of higher nervous activity play a major role both in the development of vibration disease and in the response to a single exposure to vibration (Usenko, 1961; Sirotina and Kharicheva, 1959; Shpil'berg, 1962; Livshits, in this collection; Kuznetsova, in this collection). It is evident from the foregoing that local, general single, and chronic exposure to vibration result in distinct CNS disorders. However, after local vibration the first to suffer seem to be the nerve endings and conductors, spinal cord, and sympathetic ganglia (Vaynshteyn, 1937; Gratsianskaya, 1947; others). After general vibration the first to be pathologically affected are the higher divisions of the CNS, the process being of the "neurosis" type. A single exposure to vibration can produce these changes, but the development of vibration disease is possible only after prolonged chronic exposure. 70

This gives rise to the question of whether there can be adaptation to vibration. Some authors (Andreyeva-Galanina and Butkovskaya, 1960) answer in the affirmative, relying on such facts as elevation of the threshold of vibration sensitivity even during brief stimulation and increase in muscular strength. Others, however, take a more cautious view. For example, E. A. Drogichina (1961) thinks that compensatory reactions of the organism are not impaired during the initial phase of vibration disease when all the changes are still reversible.

However, the main evidence cited by Andreyeva-Galanina and Butkovskaya in favor of adaptation can be interpreted in a very different fashion. According to the data of these and other authors, the loss of vibration sensitivity progresses after repeated exposure. It results from an alteration of the receptive fields, i.e., what seems to take place here are not adaptation phenomena but the development of a pathological process of parabiogenic character in the cutaneous contact receptors.

However, muscular strength grows, apparently because of increase in tone of the motor center and vestibular apparatus in response to an adequate stimulus such as vibration. An intensification of electric activity in muscles of the rear extremity that persists as long as 10 days after exposure was demonstrated by Z. I. Apanasenko. Several investigators directly confirm the absence of adaptation and stress the cumulative effect of vibration (Borshchevskiy, Yemel'yanov and Koreshkov, 1958; Gorbachevskiy, 1959; Volkov, 1959).

The results of our investigations also favor the view that adaptation does not occur. The compensatory mechanisms can apparently overcome temporary local processes after irregular general or local vibration, owing to the plasticity of the cortex. This may also explain the occasional instances of improved efficiency of the nerve cells noted in experiments with repeated vibrations.

Eventually, however, as cortical activity weakens, decompensation develops and the pathological processes become more pronounced.

The main factor in the development of the pathological process seems to be the relationship between intensity of the stimulus and time of "rest," i.e., the length of the interval between exposures. This is borne out by the studies of N. I. Galat (1960), who showed that repeated fractional vibration produces fewer changes in the CNS than does a single prolonged exposure. The phenomenon can be easily explained by exhaustion of the compensatory mechanisms, which are partly restored after fractional vibration. Thus, the pathological changes in the higher divisions of the CNS (the most vulnerable) that develop after /71 chronic general vibration follow the pattern of Pavlov's circular neurosis.

We are now able to elucidate, at least in part, the central mechanism responsible for the changes that arise after vibration.

Vibration sensitivity is controlled by three centers--spinal, thalamic and cortical. Thus, there are two possible ways for the pathological process to develop in the CNS. On one hand, there can be direct stimulation of the vestibular apparatus for which vibration is an adequate stimulus (Shpil'berg, 1962). As a result, a pathological focus arises in the region of the central vestibular nuclei lying in the tegmentum of the pons varolii and paralleling the external angle of the rhomboid fossa, the functioning of the brainstem reticular formation and closely connected structures of the diencephalon is impaired, and cortical-subcortical relations are disrupted.

On the other hand, nerve impulses may also travel from the various proprio-, extero-, and interoceptors, when stimulated by vibration through the spinal cord.

The spinal center of "vibration sensitivity" has been shown to extend from C₂ to D₈. It is now considered an established fact that involvement of the

spinal cord in vibration disease is a matter of parabiosis, i.e., persistent excitation of the centers. The presence of a stagnant focus of excitation in the spinal cord results in excitation spreading to the adjacent centers in accordance with the laws of irradiation. This may also account for the numerous autonomic changes that appear after exposure and are particularly marked during vibration disease.

The fact that the centers of "vibration sensitivity" in the spinal cord are adjacent to the vasomotor centers of the arms and to the interruption points of the pain and thermal sensitivity fibers (Andreyeva-Galanina, 1956) gives rise to spasm of the superficial and deep-lying blood vessels as the initial response to vibration.

Moreover, since the centers of "vibration sensitivity" are physically near the centers of gastric secretion, neurotic states create the preconditions for the development of gastric ulcer (at least in persons with an unbalanced type of nervous system).

The spread of excitation of the spinal vibration centers to the lateral horns of the spinal cord promotes degenerative changes in tissues of the extremities, etc.

Finally, stagnant excitation in the spinal cord may also radiate to /72 the cerebral cortex, which, in turn, affects the state of the cortical and sub-cortical centers. The development of this process is shown schematically in the illustration.

The diagram does not show how the various regions of the cortex are interconnected, nor does it indicate the numerous ways in which vestibular-autonomic reaction can affect the cortex. But it does show the possibility of stagnant foci of excitation forming in the spinal cord and higher divisions of the CNS.

Parabiotic processes are reversible. Despite the pronounced reaction of the CNS and other systems to brief and irregular vibration, their function eventually becomes normal. Consequently, the failure to do so after chronic vibration points to degeneration resulting from systematic and sustained injury to organs and tissues.

In examining the mechanism of action of vibration, we must try to de- /73 termine the primary processes responsible for the subsequent development of the familiar symptoms of vibration disease.

We can now speak with some assurance, first, about the direct mechanical effect on cells in various tissues and, second, about the early physicochemical changes in protoplasm.

For example, Denny-Brown and Brenner (1944) showed that a single exposure to vibration may directly damage the myelin septa of the isolated nerve and areas where myelin turns into endoneurium.

While investigating the effect of local vibration, A. Ye. Shcherbak (1908) observed hemorrhages in the spinal cord. Ye. Ts. Andreyeva-Galanina and V. G. Artamonova (1963) found degenerative changes in the gray and white matter of the spinal cord and in the brain after a single exposure to vibration.

Prolonged contact with vibration, according to L. Ch. Minetskiy (1960), causes hemorrhages and pooling of blood in the spinal cord, impairment of mineral metabolism in bones and structural deformity of bones and vertebral column.

N. I. Karpova (1963), after applying local vibration for 47 days to the paws of rabbits, noted morphological changes in different portions of the nervous system. There were degenerative changes in the axons and medullary sheaths of the nerves and swelling and vacuolation of cytoplasm along with disintegration or degeneration of individual bundles of nerve fibers and breakdown of myelin in Schwann cells. Reactive changes were noted in the cells of the anterior, lateral and posterior horns of the spinal cord gray matter. The spinal cord and membranes were characterized by vasodilatation and hyperemia, hemorrhages in the white matter and demyelination in the roots of the spinal cord.

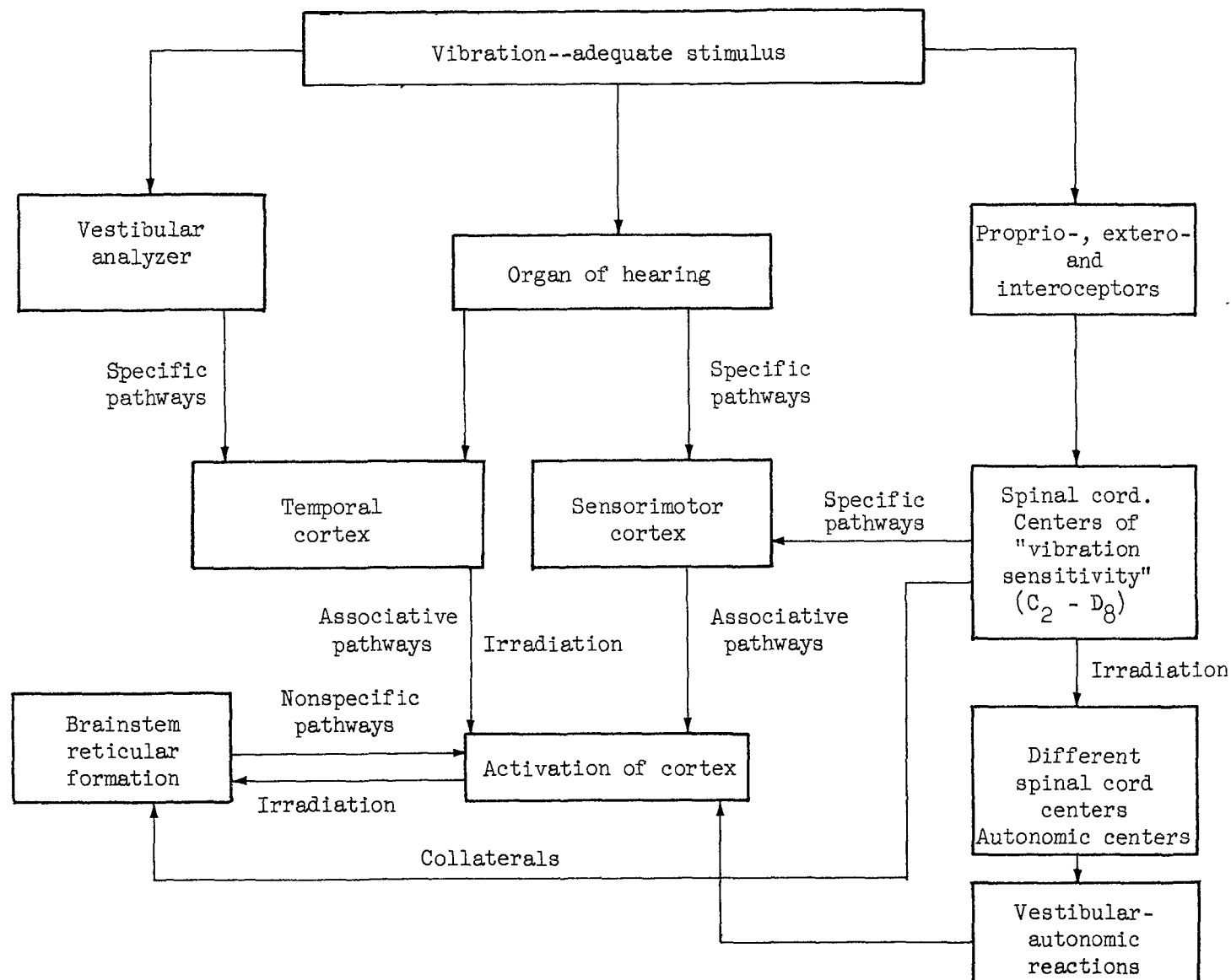


Diagram showing ways in which stagnant foci of excitation following vibration may be formed in CNS.

However, D. N. Nasonov and K. S. Ravdonik (1947) showed that paranecrotic reactions occur in the protoplasm of muscle fibers and nerve cells in the spinal ganglia after mechanical vibrations at sonic frequency. This reaction is general and unidirectional for many tissues either in vitro or in vivo (Kondrat'yeva, 1934; Shevts and Kuz'mina, 1956). Shevts and Kuz'mina observed distinct changes in protoplasm after exposure to vibration. These changes consisted of increased sorption capacity of the cells and intense and diffuse staining instead of granulated staining. This process, according to Nasonov, reflects the paranecrotic state of the cell.

Thus, the primary disruptions in living cells are due to mechanical /74 as well as to biochemical changes, which vary with the intensity of stimulation and resemble the thixotropy of colloids (Nasonov and Aleksandrov, 1940; Sroka, 1951).

However, in studying the reaction of the integral organism and neuro-humoral influences on the course of various processes, we cannot ignore the possibility of the reflex action of vibration even on the development of the primary processes. According to Shevts and Kuz'mina (1956), the exclusion of cerebral or spinal function led to the disappearance of the paranecrotic phenomena that arose after vibration, or at least they were much less pronounced than in normal animals.

These experiments demonstrated the undoubted influence of the nervous system on tissue reaction.

Vibration, therefore, is an extremely potent factor.

In this brief and incomplete account of the phenomena that arise after contact with vibration, attention was focused mainly on the processes that take place in the nervous system. But pathological changes also occur elsewhere. As mentioned before, the responses following the direct or reflex action of vibration are highly varied and embrace virtually all the systems of the organism. Those of the peripheral and central nervous systems form a prominent part of this complex. Moreover, vibration seems to be an adequate stimulus for many of the systems. On the basis of the available data, we can state quite categorically that this kind of stimulus has a direct effect on the vestibular, auditory, motor and cutaneous systems.

The subject requires further consideration and careful study. It would be extremely worthwhile, for example, to ascertain the relationship between vibration and auditory sensitivity.

As we have already seen, the principal frequencies that lead to the development of pathological phenomena are in the low and medium range (20-350 cps). Thus, sensitivity to vibration and to noise in this frequency region is similar.

Since in the course of phylogenesis the organ of hearing was formed from ectoderm, from which the skin also developed, it is reasonable to assume that the latter has preserved structures that perceive vibrations by direct contact with them. Some time ago D. N. Nasonov mentioned that there may be /75

specific contact receptors for mechanical vibrations as distinct from distant receptors that perceive vibrations through the air.

We still know little about the significance of the various analyzers in the development of the pathological process initiated by vibration, about the possibility of adaptation to it or about the nature of the compensatory mechanisms activated by such stimulation, etc.

The role of the individual physical parameters of vibration (frequencies above 250-300 cps), amplitude, etc., also has not been fully elucidated.

All this, plus the endless opportunities now available for living organisms to come into contact with sources of vibration, shows why it is essential that we gain deeper insight into the mechanism of the action of vibration.

EFFECT OF GENERAL VERTICAL VIBRATION ON VESTIBULAR
FUNCTION IN GUINEA PIGS

Z. I. Apanasenko

ABSTRACT

The influence of total vertical vibration on the functional state of the equilibrium organ was studied. Electromyograms of the group of antigravitation muscles of guinea pig hind extremities at relative rest and at adequate stimulation of equilibrium organ were recorded.

After vibration a statistically significant increase of spontaneous electrical activity of investigated muscles at relative rest was observed. Electromyographic response to adequate stimulation of the equilibrium organ was activated: latency of this reaction decreased, while after-effect prolonged it. These effects were observed 7-12 days after vibration.

General state of the animal and the cells of the peripheral blood were not subjected to statistically significant changes under the action of vibration.

A great deal of information is now available on the effects of vertical vibration. Resultant abnormalities spread to many important functional systems. For example, V. S. Georgiyevskiy and Ye. M. Yuganov (1962) observed elevation of blood pressure and increase in the cardiac rate of dogs exposed to vibration (7.7 g), although there was no change in the respiratory rate. Other authors noted the occurrence of vasospasm (Donaskaya and Stoma, 1960), intensification of intestinal peristalsis, and increased gastric tone (Mogendovich, 1961), and many other changes after vibration.

S. I. Karchmazh (1960) noted an increase in oxygen consumption proportional to the frequency and amplitude of the vibrations.

Vibration induces both functional and cytological changes. It may impair mitosis and cause the chromosomes to adhere to one another (Arsen'yeva et al., 1962).

Ya. L. Glembofskiy and G. P. Parfenov (1962) found that vibration increases the frequency of lethal mutations in *Drosophila* spermatozoa and spermatids. It is interesting to note that they also observed such phenomena after space flight. The authors think that vibration is a major contributing factor in such changes.

Of considerable significance, especially for space travel, is the effect of vibration on the central nervous system. Functional impairment of the central and autonomic systems were observed by O. Ye. Sirotin and L. M. Kharichev (1959) after vibration with a frequency of 30-36 cps. Vibration may reduce the intensity of the basic nervous processes and disrupt their normal relations (Andrianov, 1958; Mikheyeva, 1950), lengthen the latent period of reflexes and time of the aftereffect (Skachadub, 1957; Galat, 1950), and inhibit, distort and 177 sometimes completely eliminate conditioned reflexes (Butkovskaya, 1957). It also increases the number of mistakes in performing complicated psychomotor tasks (Catterson, 1962).

At the present time, however, attention is centered on the effect of vibration on the vestibular apparatus and antigravitational muscles because of the great demands made on this system during space flight.

Relevant clinical studies are very meager (Usenko, 1961; Zagryadskiy, 1957). The problem is still moot and calls for more research.

The purpose of this work was to investigate the effect of vibration on vestibular function in guinea pigs (males weighing 350-500 g).

The experimental animals (10) were examined during the 10-14 days preceding exposure, exposed, and then kept under observation for 15-20 days.

The vibration was vertical, with a frequency of 70 cps, amplitude of 0.4 mm and lasted 15 min. It was applied twice on two consecutive days.

Vestibular function was judged from the electromyographic reaction of the flexors in the hind legs of the animals under normal conditions, during adequate stimulation of these muscles and immediately afterward. As adequate stimulation we used graduated rocking of the animal around the longitudinal axis of the body on a special apparatus for 10 sec with a frequency of 0.6 of a cycle and inclination angle of 25°.

As the electromyograms were being recorded on film, they were integrated by means of a special integrator and expressed in relative units from the readings of a mechanical register.

The peripheral blood, weight, temperature and general condition of the animals were observed simultaneously with the electromyographic investigation.

The resultant data were processed by the method of nonparametric statistics.

The myograms recorded before vibration were fairly similar in all the animals. While the animal was sitting quietly in its normal position, oscillations of potential with an amplitude of 10-50 μ v were more or less uniform.

Volleys of impulses with a large amplitude (150-350 μv) appeared simultaneously on the EMG with each test rocking during adequate stimulation of the vestibular apparatus (fig. 1). The aftereffect of the reaction to vestibular stimulation was reflected on the EMG either in preservation of 3-4 volleys ^{/78} of heightened electric activity, or in a general uniform increase in amplitude of the muscle currents. The average duration of the aftereffect was 2-4 sec. The latent period of this reaction was roughly 0.1-0.3 sec.

Thus, the mean integral values of electric activity remained at about the same level in the control animals throughout, and in the experimental animals before application of vibration with slight fluctuations in either direction from the mean norm. This was true both for the period of rest and for the period of reaction to adequate stimulation of the vestibular apparatus and during the aftereffect. The levels of integral electric activity during the reaction to vestibular stimulation exceeded the level of electric activity in the resting animal 3-5-fold and during the aftereffect of this reaction, 1.5-3-fold. These correlations may be considered normal for proper and adequate functioning of the guinea pig vestibular analyzer.

Vibration produced significant and fairly persistent changes in the animals at rest and while responding to vestibular stimulation. The amplitude of the

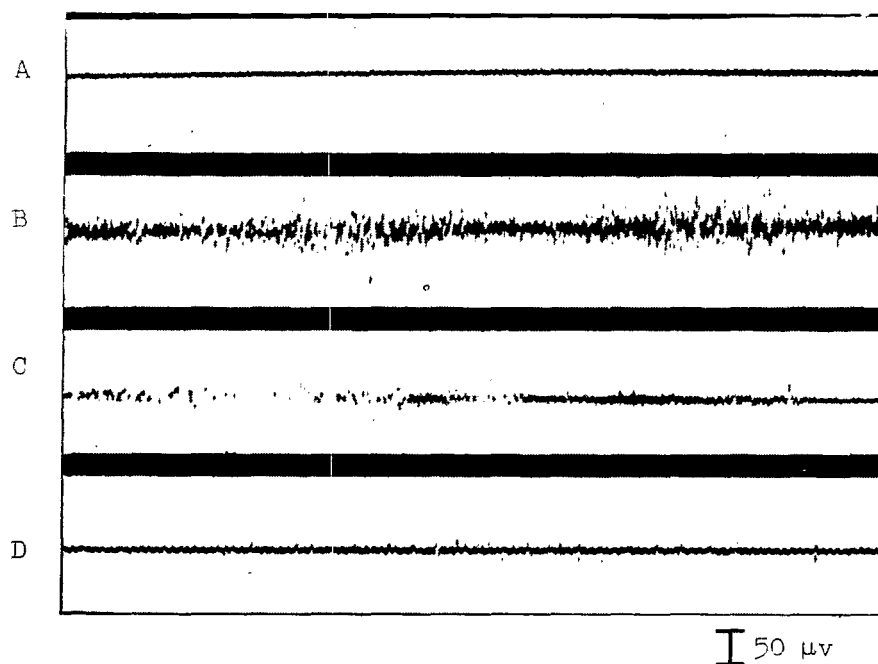


Figure 1. Normal appearance of EMG of muscles in hind leg of guinea pig at rest during and after test rocking. A--background; B--reaction to test rocking; C--aftereffect (volleys of impulses); D--aftereffect (solitary impulses).

muscle currents increased and the shape of the EMG changed somewhat. The observed phenomena were easily analyzed from the change in integral electric activity of the muscles under study.

Figure 2 shows the dynamics of changes in integral electric activity of muscles in the hind legs of guinea pigs at relative rest. The data are averaged for both experimental and the control animals. The integral electric activity is expressed in units of deviation from the mean norm (in the graph the mean norm is taken as 0) and related to the mean deviation from the norm before vibration for each group of animals. This makes it possible to distinguish only those changes which clearly exceed the level of the mean value and the mean deviations from this value before vibration.

The figure clearly shows that background myoelectric activity increased under the influence of vibration. The changes were particularly marked immediately after exposure. Their persistence was noteworthy. Apparently weak action kept the background electric activity at an abnormally high level for at least 5 days: in some animals for 10-15 days afterward. The observed changes were statistically significant with a probability of $P < 0.01$ (relative to the original background and to the mean data in the control animals). /80

Of the entire group of experimental animals, only one failed to exhibit increased myoelectric activity while at relative rest, and there was even a tendency for the level of bioelectric activity to drop.

Figure 3 shows changes in myoelectric activity of the experimental and control animals during adequate stimulation of the vestibular apparatus by graduated rocking.

The vestibular-tonic reaction to adequate stimulation of the vestibular apparatus after vibration was fairly complex. It is evident from figure 3 that the total electric activity of the muscles during test rocking was somewhat less in the experimental animals than in the controls. The changes, to be sure, were at the boundary line of significance, but the tendency to decrease was

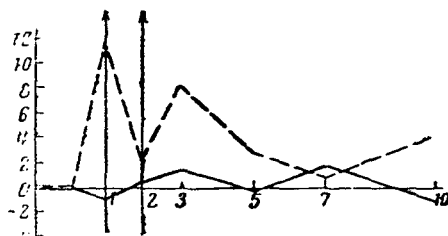


Figure 2. Change in background electric activity of muscles in hind legs of guinea pigs after vibration. Unbroken line--control group; broken line--group exposed to vibration. Abscissa--value of myoelectric activity in relative units. Arrows designate days of exposure.

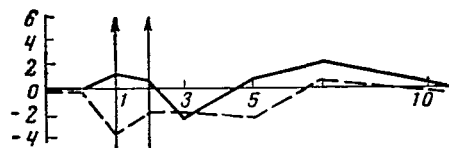


Figure 3. Changes in integral electric activity in muscles of hind legs of guinea pigs on adequate stimulation of vestibular apparatus after vibration. Symbols same as in figure 2.

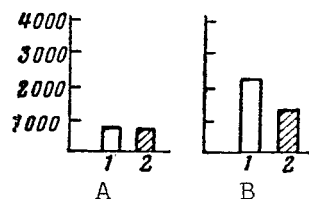


Figure 4. Spread of values of electric activity of muscles in hind legs of guinea pigs during test stimulation (A) before and (B) after vibration. 1--control group; 2--experimental group. Figures on abscissa--value of variance.

quite pronounced. Meanwhile the EMG reaction to adequate stimulation not only decreased, but apparently stabilized, with a narrowing of the spread of values of the electric activity. After vibration the variance became less than in the control group (fig. 4).

All experimental animals reacted to vibration in a similar fashion. More or less the same relations also appeared in the aftereffect of the reaction (fig. 5).

Myoelectric activity in the aftereffect decreased somewhat under the influence of vibration, just as it did during the reaction itself. This was particularly noticeable on the day of exposure. On subsequent days electric activity changed in wavelike manner, but the curve for the experimental group continued to remain a little below the control curve. The changes were marked, but statistically insignificant ($P > 0.05$ both in the median and in the variance). The spread of the values of electric activity also narrowed in this case (it was less for the experimental animals than for the controls).

The slight lowering of the level of myoelectric activity noted during the reaction and aftereffect thereof could presumably be attributed to the development of adaptation by the vestibular analyzer after vibration. In this case the test rocking might have elicited impulses of smaller amplitude than before adaptation. However, this assumption is not very likely because vibration

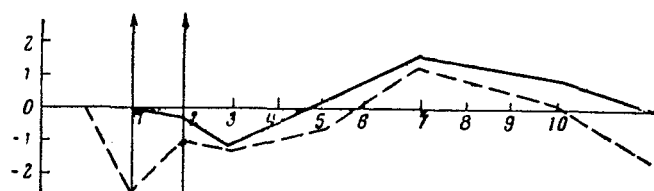


Figure 5. Changes in integral electric activity of muscles in hind legs of guinea pigs in aftereffect of reaction to test stimulation after vibration.
Symbols same as in figure 2.

was applied briefly (twice for 15 min each time), and adaptation could scarcely have occurred.

Another reservation is that in processing the data the absolute values (from the register) of myoelectric activity for the reaction and aftereffect among the experimental animals were related to too high a background after vibration, so that the actual level of electric activity at these periods of the investigation could have been too low.

The complex nature of the influence of vibration on the vestibular reaction is seen in the fact that despite rather low total myoelectric activity during the reaction proper and its aftereffect, the latent period of the reaction was considerably shortened while the duration of the aftereffect increased.

The extent of the latent period and duration of the aftereffect of the reaction to adequate stimulation of the vestibular apparatus were determined from the electromyographic tracings on the film (fig. 6).

Under the influence of vibration the latent period of the reaction was considerably reduced, especially right after the action. It was not until 5-7 days after vibration that the duration of the latent period rose to the level of that in the control group. Meanwhile, the spread of values of the latent period, although greater than the control, was not very significant (from the variance test $P > 0.05$). However, the central direction of the changes here differed quite significantly ($P < 0.01$) from the control (the median shifted markedly toward the lower values).

The changes were the same in all experimental animals.

A similar pattern is shown in figure 7, which contains a graph of the mean values of the latent period after exposure in percentages of the mean values before exposure.

In the control, the mean duration of the latent period of the electromyographic reaction to test rocking scarcely changed, but after vibration it decreased appreciably. The differences from the control were significant ($P < 0.05$). /82

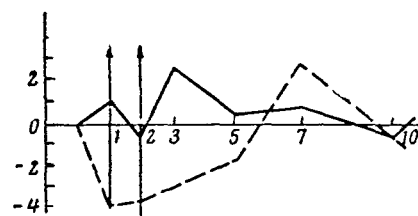


Figure 6. Change in duration of latent period of reaction to adequate stimulation of vestibular apparatus after vibration.

Ordinate--duration of latent period expressed in relative units. Other symbols same as in figure 2.

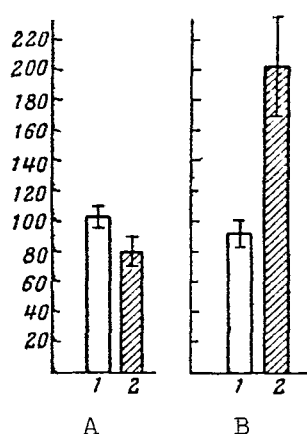


Figure 7. Duration of latent period (A) and aftereffect (B) of reaction to test stimulation of vestibular apparatus after vibration in percentages of their mean values before exposure.

1--control group; 2--group exposed to vibration. Vertical lines designate triple statistical error of mean value.

Figure 8 shows the effect of vibration on the duration of the aftereffect of the reaction to adequate stimulation of the vestibular apparatus. Vibration caused a persistent and sharp lengthening of the aftereffect, which was significantly different from the control, both in spread of values and in central direction (both in the variance and in the median $P < 0.01$). The changes were similar for all experimental animals and persisted for 10-15 days after exposure.

The graph in figure 7B shows the mean duration of the aftereffect of the reaction after exposure in percentages of the corresponding mean values before exposure. It is obvious that after vibration the duration of the aftereffect was more than double.

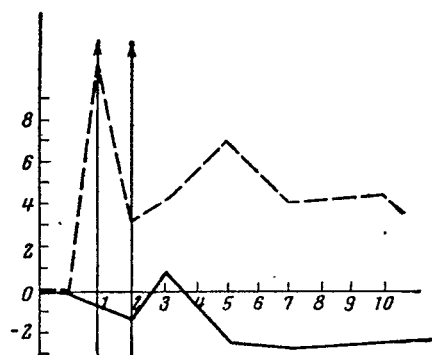


Figure 8. Changes in duration of aftereffect of reaction to adequate stimulation of vestibular apparatus after vibration.

Ordinate--duration of aftereffect expressed in relative units. Symbols same as in figure 2.

Thus, the two exposures to vibration used in our experiments caused a fairly persistent increase in electric activity of the muscles at relative rest, accelerated the electromyographic reaction to adequate stimulation of the vestibular apparatus and lengthened the aftereffect of this reaction.

No significant differences were noted between the experimental and control animals with respect to the animals' general condition, weight or peripheral blood.

The results of our investigation clearly indicate that vibration gives rise to functional changes localized in the vestibular (latent period and duration of the aftereffect of the vestibular-tonic reaction) and motor (spontaneous bioelectric activity at relative rest) apparatuses. These changes reflect fairly persistent excitation for several days after exposure.

The pertinent literature on this subject is meager and scattered, but it essentially supports our findings.

For example, V. R. Usenko (1961) noted a decrease in vestibular chronaxie and rheobase in human beings after vibration.

L. V. Donskaya and M. F. Stoma (1960) found that the amplitude of muscle biocurrents increases with acceleration (to a certain limit) of the frequency of vibration. B. M. Savin (1957) states that acceleration may create powerful foci of excitation in the cerebral cortex, chiefly in the region of the motor apparatus. /83

This conflicts with the view of Z. M. Butkovskaya (1957) that an irradiated inhibitory process develops in the central nervous system after vibration. The contradiction can be resolved, we believe, if we assume that the inhibition observed by Butkovskaya developed, like protective inhibition, through a phase

of overexcitation. Such an assumption is plausible in the light of V. A. Shebalin's finding (1962) that the lability of the nerve centers decreases after vibration.

M. A. Kuznetsova (compare her article elsewhere in this collection) observed impairment of the normal intensity relations and the appearance of parabiogenic phases in the passive defense motor reflex arc after vibration. This is an additional piece of evidence in support of our assumption.

In our investigation we used vibration with a low amplitude and comparatively low frequency which, according to the literature (Zagryadskiy, 1957; Mogendovich, 1961), acts on the body chiefly through the vestibular apparatus, suggesting that the changes we observed in the vestibular apparatus-antigravitational muscle system are regular, and that it was precisely here that abnormalities could naturally be expected to arise. /84

A final point of interest is that the changes in vestibular function after vibration are similar to those which we found in the guinea pigs flown on the fourth spacecraft (Apanasenko and Kuznetsova, 1963).

Conclusions

1. Two 15-minute exposures of guinea pigs to vibration cause a statistically significant increase in the spontaneous electric activity of muscles in the hind legs, while the animals are in a state of relative rest.

2. The same vibration elicits an electromyographic reaction to adequate stimulation of the vestibular apparatus--the latent period of this reaction decreases, but the aftereffect increases.

3. These changes persist for 5-7 days after vibration.

4. The general condition of the animals and composition of the peripheral blood under the influence of vibration do not undergo statistically significant changes.

EFFECT OF ACUTE WHOLE-BODY γ -IRRADIATION ON VESTIBULAR FUNCTION IN GUINEA PIGS

Z. I. Apanasenko

ABSTRACT

The change in functions of the equilibrium organ of guinea pigs totally irradiated with γ -rays Co^{60} with 500 r, at a dose rate of 261 r/min, was studied. Electromyograms of the group of antigravitational muscles in hind legs of guinea pigs at relative rest and at adequate stimulation of equilibrium organ were recorded. After irradiation a distinct decrease of spontaneous electrical activity of the investigated muscles at relative rest and the change of bioelectric reaction of these muscles to the adequate stimulation of the equilibrium organ were observed. This reaction becomes less regular and often is pathologically increased; its latency increases sharply, while aftereffect is shortened. The clinical state of the animals was in conformity with the normal course of acute radiation sickness with lethal outcome on the 9th-14th day.

The effect of penetrating radiation on vestibular function has received little study to date. The literature is not only sparse, but extremely contradictory. For example, N. V. Moskovskaya (1959) noted under clinical conditions an increase in vestibular excitability during and after X-irradiation with a dose of 5000-12,000 r (exposure of the cervical or thoracic region). Yu. G. Grigor'yev (1962) found, however, that the excitability of the vestibular apparatus regularly decreases after massive doses of radiation. A. A. Sveshnikov and A. V. Sevan'keyev (1962) showed that the excitability and reactivity of the vestibular apparatus decreases after a dose of 200 r, and that doses of 500-5000 r result in severe inhibition of labyrinthine function. /85

The purpose of our investigation was to study changes in vestibular function after acute whole-body exposure to 500 r doses of the γ -rays of Co^{60} at a dose rate of 261 r/min.

The experimental animals were guinea pigs weighing 350-500 g. The electromyographic reaction of the antigravitational muscles in the animals' hind

legs to adequate stimulation of the vestibular apparatus by graduated rocking served as a criterion of vestibular function.

The method of adequate stimulation and the technique of recording and processing of the data are described in an earlier article.

Along with the electromyographic investigation we observed the peripheral blood, weight, temperature, general clinical condition and survival rate of the animals.

All data were statistically processed. The experimental animals (10) were examined 1-2 weeks before exposure and thereafter until they died (after 10-15 days). The control animals (5) were examined at the same times. /86

All electromyograms of the experimental animals before exposure and those of the controls throughout the experiment had a normal appearance. The general integral level of electric activity for each of the periods studied (relative rest, reaction to adequate stimulation of the labyrinths and aftereffect thereof), duration of the latent period and aftereffect of the reaction also were normal and quite stable.

After exposure the amplitude of the muscle currents frequently decreased, the electromyograms were reduced and their form became altered.

The observed phenomena are best analyzed, however, from the changes in integral electric activity. Figure 1 shows the changes in background (at rest) integral electric activity of the muscles after irradiation. The curves were plotted from figures averaged for all animals of each group.

It is evident from figure 1 that irradiation caused a prolonged decrease in the electric activity of the muscles at relative rest. In 2 of the 10 animals in this group, background electric activity did not decrease after irradiation; in fact it even increased slightly. It is interesting to note that this high level of muscle activity at rest persisted in these animals until they died. In the other 8 guinea pigs, however, myoelectric activity was very low until they died. The changes averaged out for the experimental animals lying on the borderline of statistical significance ($P < 0.05$ both in the median and in the variance), but the general tendency for the background bioelectric activity of the muscles to decrease was quite apparent.

Irradiation resulted in inadequate pathological heightening of the electromyographic reaction to the test stimulation (fig. 2). This increase was particularly characteristic of the more remote periods after irradiation. It will be noted, however, that the results varied from animal to animal. Some of them exhibited a reaction to rocking that was either somewhat too strong or /87 too weak. Two animals responded very weakly throughout the observation period to adequate stimulation of the vestibular apparatus. In 5 animals, the level of electric activity fluctuated from day to day, now considerably above normal, now somewhat below. The other 3 guinea pigs maintained a fairly high level of myoelectric activity. On the second or third day after irradiation, the level of myoelectric activity was quite low in almost all animals. Just before they died, it dropped sharply in all. Statistical processing of these

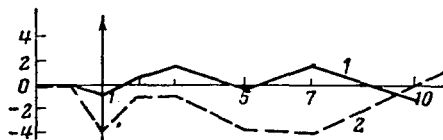


Figure 1. Change in background activity of muscles in hind legs of guinea pigs after irradiation. 1--control group; 2--irradiated group. Abscissa--time after irradiation in days; ordinate--magnitude of electric activity expressed in relative units. Arrow designates day of irradiation.

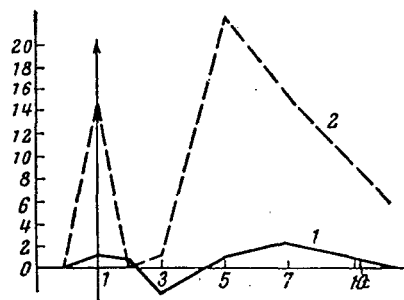


Figure 2. Change in integral electric activity of muscles in hind legs of guinea pigs during adequate stimulation of vestibular apparatus after irradiation. Symbols same as in figure 1.

data showed that the changes noted were significant. Although the spread of values increased markedly after irradiation (in the variance $P < 0.001$), their central direction changed insignificantly. The varied and unstable nature of the postirradiation changes observed in the reaction to stimulation of the vestibular apparatus is also evident in figure 3, which shows a substantial increase in the variance for the values of the reaction in the irradiated animals.

Figure 4 shows the change in integral electric activity of muscles in the aftereffect of the reaction to test vestibular stimulation. The aftereffect period was characterized by wavelike change in the values of electric activity. It decreased the first few days after irradiation, increased on the third day, then decreased and so on.

The curve for the group of irradiated animals differed significantly from the curve for the control both in central direction (for the median $P < 0.01$) and in spread of values (for the variance $P < 0.005$).

In addition to these indices, we were also able to use the EMGs on film to measure the length of the latent period and duration of the aftereffect of the reaction to test stimulation of the vestibular apparatus.

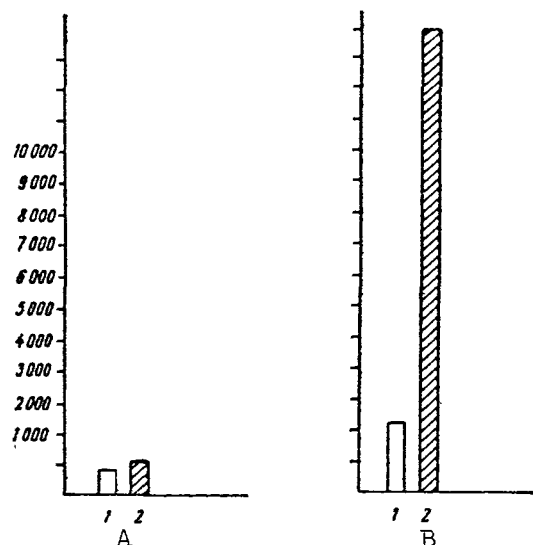


Figure 3. Variance of the values of electric activity of muscles in hind legs of guinea pigs during vestibular stimulation (A) before and (B) after irradiation. 1--control group; 2--irradiated group. Number on ordinate--values of the variance.

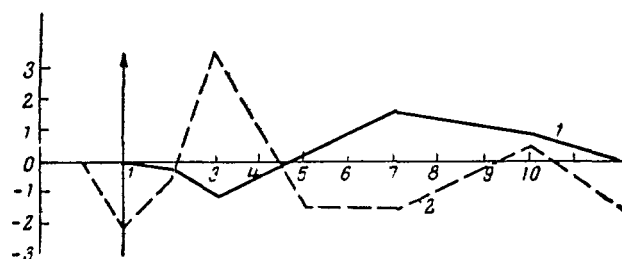


Figure 4. Change in integral electric activity of muscles in hind legs of guinea pigs in aftereffect of reaction to vestibular stimulation after irradiation. Symbols same as in figure 1.

Irradiation caused a persistent lengthening of the latent period of the reaction to adequate stimulation of the vestibular apparatus (fig. 5). In /89 this case the differences from the control group were absolutely significant according to the variance test ($P < 0.01$), and they lay on the borderline of significance ($P < 0.05$) according to the median test, apparently by virtue of the tendency for the latent period to lengthen slightly in the control.

Figure 6 clearly shows that after irradiation the latent period of the EMG reaction to adequate stimulation of the vestibular apparatus lengthened

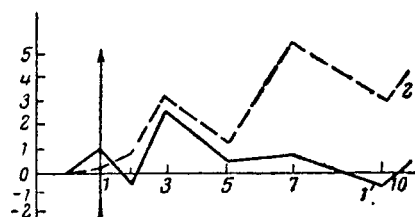


Figure 5. Change in duration of latent period of reaction to adequate stimulation of vestibular apparatus after irradiation.

Ordinate--length of latent period expressed in relative units. Symbols same as in figure 1.

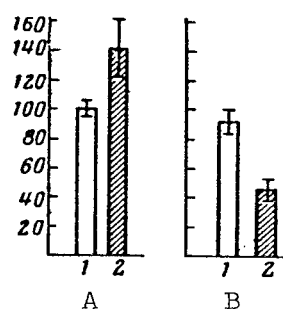


Figure 6. Duration of latent period and aftereffect of reaction to adequate stimulation of vestibular apparatus after irradiation in percentages of their mean values before exposure.

A--latent period; B--aftereffect; 1--control; 2--irradiated animals. Vertical lines designate triple statistical error of mean value.

considerably. While the latent period increased under the influence of irradiation, the aftereffect of this reaction in the exposed animals shortened quite markedly (fig. 6B).

The aftereffect scarcely changed in the control animals (it shortened by 7 percent). In the experimental animals, however, it shortened after irradiation almost twice as much.

Figure 7 shows the dynamics of the duration of the aftereffect of the myoelectric reaction to vestibular stimulation by the days after irradiation. Here it is also obvious that irradiation shortened the aftereffect of this reaction. The changes were significant and they persisted throughout the observation period, although the differences from the control in this figure are less instructive than those in figure 6.

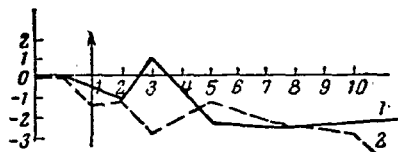


Figure 7. Change in duration of aftereffect of reaction to test stimulation of vestibular apparatus after irradiation.

Ordinate--duration of aftereffect expressed in relative units. Other symbols same as in figure 1.

Thus, it is fair to conclude from the foregoing that under the influence of acute radiation the reaction to adequate stimulation of the vestibular apparatus becomes inhibited, less distinct and irregular. Although myoelectric activity during this reaction was pathologically high, the latent period of the reaction increased, while the duration of the aftereffect was reduced.

As for the state of the peripheral blood, the control animals exhibited, starting the second to third day after irradiation, the decrease in leukocyte count characteristic of acute radiation sickness. This decrease (sometimes with temporary increases) was statistically significant. Before the animals died, the leukocyte count dropped in some cases to 700-500 in 1 mm³ of blood.

Radiation sickness was accompanied by a statistically significant /90
weight loss.

The animals died 9-14 days after exposure, with symptoms of radiation pneumonia and hemorrhages in the subcutaneous tissue and viscera. All the controls and only one experimental animal survived.

Our findings suggest that the functions of the vestibular-motor system of guinea pigs are inhibited under the influence of acute whole-body γ -irradiation. Background myoelectric activity decreases, the latent period of the test reaction grows and the duration of the aftereffect shortens. The abnormally high myoelectric activity noted in some animals during test rocking was, in our opinion, pathological and another indication of the decrease in efficiency of the vestibular apparatus after irradiation.

Our data, therefore, are consistent with the findings of those authors (Sveshnikov and Sevan'keyev, 1962; Grigor'yev, 1962; and others) who observed that the excitability and reactivity of the vestibular apparatus decreases after irradiation. The tests used by these authors (rotation with acceleration, caloric and other clinical tests) were addressed mainly to the semicircular canals, whereas our test largely stimulated the otolithic apparatus. The coincidence of the results in both cases shows that the two main structures of the vestibular apparatus (otoliths and semicircular canals) suffer a similar alteration of function as a result of penetrating radiation.

The heterogeneity and lack of synchronism of the data noted in the experimental animals may well have been due to their individual characteristics.

/91

Conclusions

1. Acute whole-body irradiation of guinea pigs with 500 r of Co⁶⁰ causes a distinct decrease in spontaneous electric activity of the antigravitational muscles in the hind legs.

2. The bioelectric reaction of these muscles to adequate stimulation of the vestibular apparatus becomes irregular and sometimes pathologically high under the influence of irradiation. The latent period of this reaction lengthens markedly, but its aftereffect shortens. The changes are statistically significant.

COMBINED EFFECTS OF VIBRATION AND ACUTE IRRADIATION ON VESTIBULAR FUNCTION IN GUINEA PIGS

Z. I. Apanasenko

ABSTRACT

The complex effect of simultaneously or consecutively applied vibration and acute irradiation with a dose of 500 r on the functions of the equilibrium organ was studied. Electromyograms of the group of antigravitational muscles of guinea pig hind extremities at relative rest and at adequate stimulation of equilibrium organ were recorded.

The change in radiation response of the organism under vibration effect was recorded. Under combined effect of these factors, electrical activity of muscles at relative rest does not decrease as under a single irradiation; on the contrary, it increases. The change of electromyographic reaction to adequate vestibular stimulation characteristic of radiation effect is absent. The latency of this reaction increases, not at once, but only close to the death of the animals; the aftereffect increases at first, and only a week after the exposure it sharply decreases.

By the number of blood cells, weight dynamics, general clinical state and animal survival, the author found no authentic differences between complex effect and single irradiation.

The combined effects of vibration and penetrating radiation on the organism have been scarcely studied, even though the importance of the problem becomes more evident with each passing day. Radiation and vibration are active agents, capable of inducing marked functional changes in different systems of the body. Moreover, whether they are applied simultaneously or consecutively, each may significantly alter the systemic reaction to the other. Thus radiation reactions may be quite surprising. /92

There are only a few published reports describing the combined effects of radiation and centrifugation or vibration on the survival rate of animals.

Taylor (1960) exposed rats to 600 r of radiation and 7 min of centrifugation with an acceleration of 20 g. No differences were noted in survival rate as between the irradiated animals and the animals subjected to combined action

This was also the result of another experiment, in which animals irradiated with Co^{60} were centrifuged either immediately after removal of the cobalt or 10 days later (Lyle, 1961). A. N. Ganshina (1961) concluded from pathologico-anatomical investigations that vibration scarcely changes the effect of fractional irradiation, but it greatly intensifies the effect of acute irradiation.

Of considerable interest is the effect of vibration on the functional changes which arise in the nervous system as a result of penetrating radiation, especially its effect on the radiation reactions of the vestibular apparatus. High demands are made on the vestibular apparatus-antigravitational muscle 93 system during space flight.

The purpose of our work was to study the combined effects of vibration and acute irradiation on the vestibular apparatus of male guinea pigs weighing 350-500 g. The animals were divided into two groups. One (9) was exposed to irradiation once 20-30 min after vibration, and 23-24 hours later subjected to vibration again. The second group of guinea pigs (5) was the control. Irradiation was acute, whole-body, with 500 r of Co^{60} γ -rays delivered at a rate of 261 r/min.

Vibration was vertical with a frequency of 70 cps and amplitude of 0.4 mm, applied for 15 min each time.

The animals were examined 10-14 days before exposure and until they died 9-14 days after exposure.

Besides investigating the vestibular function, we checked the peripheral blood, weight, temperature, general clinical condition and survival time of the animals. All resultant data were processed by the methods of nonparametric statistics.

Vestibular function was studied by means of electro-myographic recordings from a group of antigravitational muscles (flexors) in the hind leg, following adequate stimulation of the receptors of the vestibular apparatus.

The methods of recording EMGs, adequately stimulating the vestibular analyzer and analyzing the results, have been described in the preceding article.

The combined action intensified the spontaneous background electric activity of the muscles under study. The changes persisted virtually until the animals died. Electric activity decreased only in the period preceding death. The difference from the control was statistically significant both in variance and in central direction ($P < 0.01$). The variance increased while the median shifted upward.

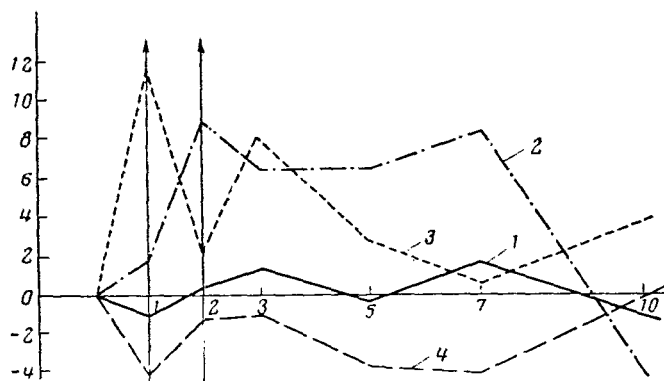


Figure 1. Changes in background electric activity of muscles in hind legs of guinea pigs after combined action. 1--control group; 2--group exposed to the combined action; 3--vibrated group; 4--irradiated group. Abscissa--time after action in days; ordinate--magnitude of electric activity expressed in relative units. First arrow designates effect of vibration and irradiation; second arrow, only vibration.

Thus, after combined action the background myoelectric activity changed in the same direction and on about the same scale as after the action of vibration alone. Vibration had such a powerful effect on the radiation reaction that it assumed the leading role in the combined action and until the predeath period masked the effect of irradiation, completely distorting its character.

The changes observed after the combined action were significantly different from those which followed irradiation ($P < 0.01$), but the differences from the results of vibration lay on the borderline of significance ($P < 0.05$).

Figure 2 shows the changes in electric activity of the same muscles during adequate stimulation of the vestibular apparatus by graduated rocking around the longitudinal axis of the body. It is clear from the graph that the changes here were wavelike in nature. The myoelectric reaction to vestibular stimulation decreased slightly the first few days after the combined action, then increased, but a little later (and until death) again decreased somewhat. The changes noted in the reaction were insignificant. The central direction of the deviations was scarcely different from that of the control, and the value of the median for the experimental animals shifted downward very slightly ($P > 0.05$). However, the changes in variance differed significantly from those in the control ($P < 0.01$).

The combined action of vibration and irradiation took an intermediate position between the isolated effect of either agent. During the first two days after the combined action, the effect of vibration seemed to predominate in the reaction (the curve proceeds in the same direction as after vibration--compare the article in this collection on the subject). But with the onset of

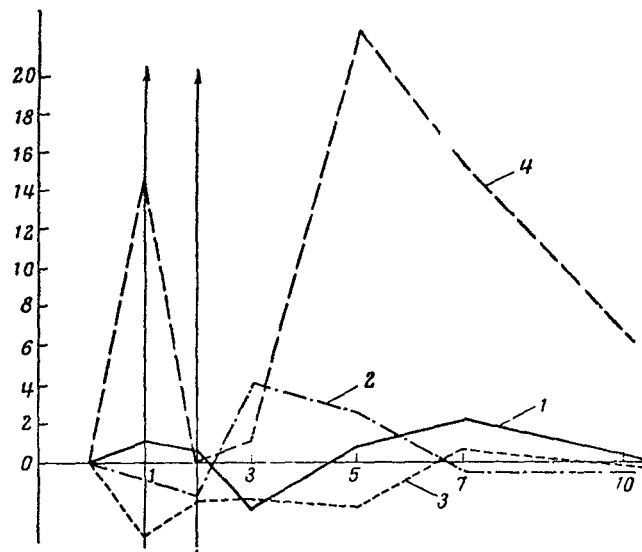


Figure 2. Changes in integral electric activity of muscles in hind legs of guinea pigs during adequate stimulation of the vestibular apparatus after combined action. Symbols same as in figure 1.

radiation sickness, the changes followed the direction of the radiation effect. The curve reflecting the results of the combined action lies above the curve of the vibration changes, but much below the curve of the radiation changes. The curve of the complex action does not differ significantly in central directivity from the vibration and irradiation curves. The median of the changes in the animals subjected to the combined action lies just a little higher than the median of the changes after vibration, and a little lower than that after irradiation. With respect to the variance test, the difference between the isolated and combined action of vibration and acute irradiation is statistically significant ($P < 0.01$). With respect to the values of the variance (fig. 3), the combined action also clearly occupies an intermediate position between the isolated and combined action of the two factors. The variance of the values of electric activity in response to vestibular stimulation after the combined action is much greater than the variance of these values after vibration but is less after irradiation.

The data are somewhat heterogeneous for individual animals in the group exposed to the combined action, but the heterogeneity follows no law, nor is it as great as after irradiation alone. There were no cases of a severe pathological intensification of the reaction to vestibular stimulation, as we observed after irradiation. 197

Changes in the integral electric activity of the muscles in the aftereffect of the reaction to test vestibular stimulation are shown in figure 4. After the combined action, myoelectric activity decreased slightly, especially during the first two days. The deviations, however, were quite insignificant,

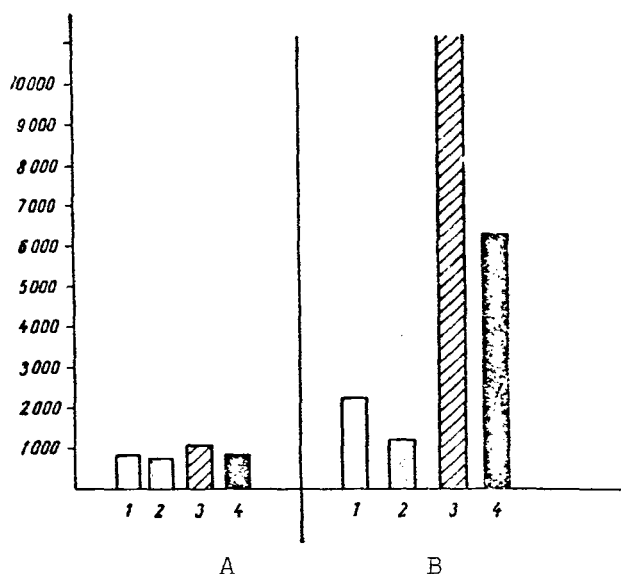


Figure 3. Variance of values of electric activity of muscles in hind legs of guinea pigs during vestibular stimulation (A) before and (B) after combined action. 1--control group; 2--vibrated group; 3--irradiated group; 4--group exposed to combined action. Figures on ordinate--values of variance.

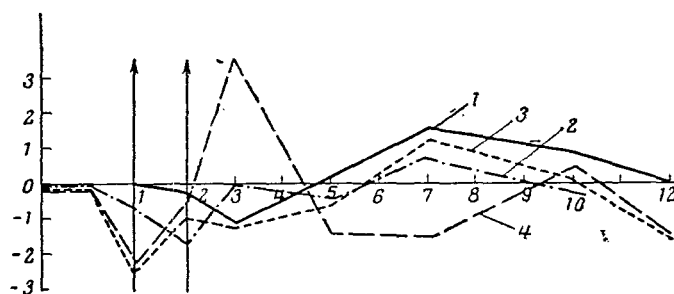


Figure 4. Changes in integral electric activity of muscles in hind legs of guinea pigs during aftereffect of reaction to vestibular stimulation after combined action. Symbols same as in figure 1.

and neither in variance nor in median did they differ significantly from the control. It will be recalled that irradiation alone effected statistically significant changes in electric activity during the aftereffect, but vibration alone did not do so. Thus, here as in the background electric activity, vibration so strongly altered the radiation effect that the influence of irradiation was almost completely concealed. Figure 5 shows the changes in duration of the

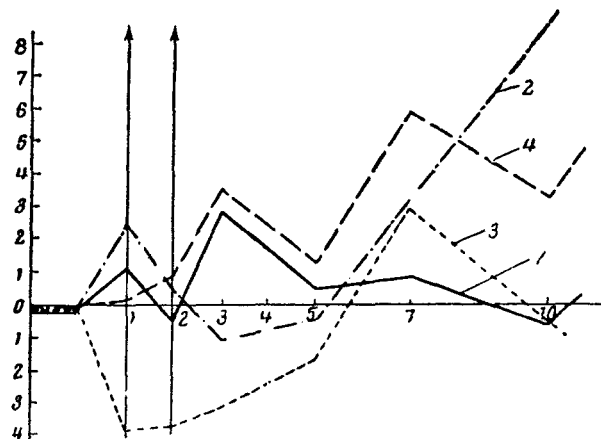


Figure 5. Changes in duration of latent period of reaction to adequate stimulation of vestibular apparatus after combined action.

Ordinate--duration of latent period expressed in relative units. Symbols same as in figure 1.

latent period of the reaction to adequate stimulation of the vestibular apparatus after the combined action.

During the first week after the combined action, the latent period of 198 myoelectric reaction remained within the range of changes in the control. Neither in central directivity ($P > 0.5$) nor in spread of values ($P > 0.05$) was there a statistically significant difference from the control. Once again we encounter the interesting phenomenon where a combined action uniting the characteristics of two factors with an opposite effect on the duration of the latent period (vibration shortens the latent period while irradiation lengthens it) does not cause changes significantly different from those in the control.

The latent period of the vestibular reaction of the animals exposed to the combined action increased sharply only after a relatively long interval of time, just before they died. Prior to death, the masking influence of vibration apparently disappeared, and the symptoms of acute radiation sickness became evident. With the combined action, vibration altered the radiation effect to such an extent that the curve reflecting the data obtained after the combined action differed significantly from that showing the changes that ensued after irradiation alone ($P < 0.01$).

The same relations can be seen in figure 6A, which presents the mean 199 values of the latent period after the action in percentages of the corresponding mean values before the action. The mean latent period was longer among the animals exposed to the combined action than among the animals subjected to vibration, but shorter than among the irradiated animals; i.e., the result of the combined action fell between the results of vibration and irradiation.

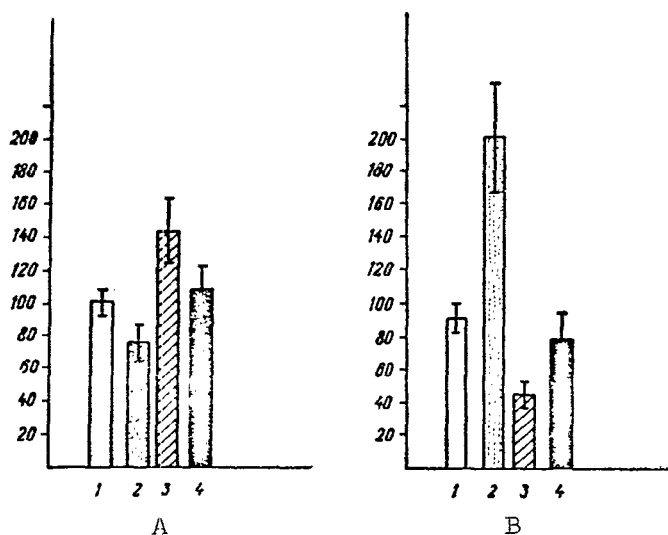


Figure 6. Duration of latent period and aftereffect of reaction to test stimulation of vestibular apparatus after action in percent of their mean values before action. A--latent period; B--aftereffect; 1--control group; 2--vibrated group; 3--irradiated group; 4--group exposed to the combined action. Vertical lines designate triple statistical error of mean value.

Thus, the mean value of the latent period of the reaction under study did not differ significantly from the control after the combined action.

The combined action was followed initially by a marked increase in duration of the aftereffect (fig. 7). Five days later it shortened considerably. Here also vibration was more prominent, and the results of the combined action were subordinated to its influence. It was only after all the symptoms of radiation sickness had become manifest, that the combined effects began to assume the characteristics of penetrating radiation. We should like to /100 point out that the increased duration of the aftereffect of the vestibular-tonic reaction typical of the first period was not as persistent as after vibration. The data on individual animals within the group are somewhat heterogeneous, like those for the first period of time.

The observed changes differed significantly, however, from the control ($P < 0.01$). Accordingly, the results of the combined action likewise differed significantly from the results obtained after the action of vibration or irradiation ($P < 0.01$).

Figure 6B shows the mean duration of the aftereffect following the combined action in percentages of the normal duration of the aftereffect.

The results of the combined action occupies an intermediate position between the results of the isolated effect of vibration and irradiation.

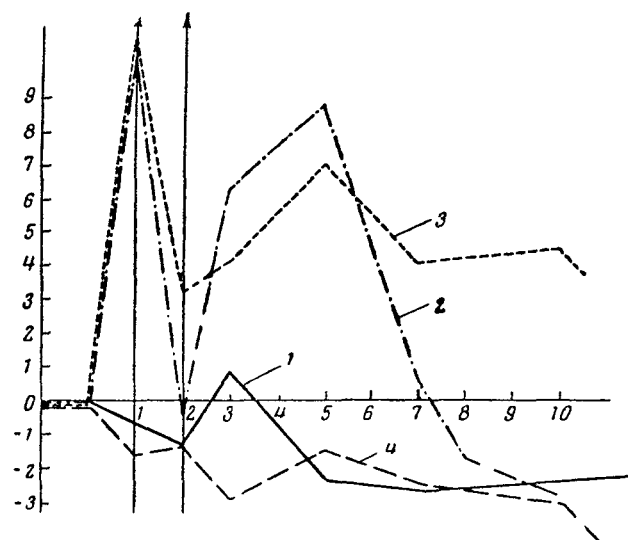


Figure 7. Changes in duration of aftereffect of reaction to adequate stimulation of vestibular apparatus after combined action. Ordinate--duration of aftereffect expressed in relative units. Other symbols same as in figure 1.

Whereas the radiation changes in the myoelectric reaction to adequate stimulation of the vestibular apparatus following the combined action were more or less obliterated by vibration, the clinical course and outcome of radiation sickness did not follow this pattern.

All animals exposed to the combined action died. The changes in peripheral blood, weight, and general condition of the animals were characteristic of acute radiation sickness. There were no spontaneous deaths among the control animals. Fluctuations in weight and composition of peripheral blood were within normal limits. The difference between the experimental and control animals was statistically significant for all these indices.

It is difficult to speak with assurance about the clinical differences from the action of irradiation alone because of the comparatively small number of animals used. We were unable to detect any significant differences between the survival rate of animals exposed to the combined action and that of animals exposed to irradiation alone, because all animals in the first group died (between the 9th and 12th days) as compared with only one in the second group. We can only say that the animals in the first group died one or two days before those in the irradiated group.

The course of the radiation sickness, judging by the general clinical condition, was more severe in the animals exposed to the combined action. There were no significant differences in weight or peripheral blood, whether the animals were exposed to the combined action or to radiation alone.

The results of our investigation indicate that when the organism is subjected to a combination of acute penetrating radiation and vibration, the latter has by far the more significant influence on the course of the radiation reactions and it distorts them. After the combined action the vibration changes were usually the more prominent. The radiation effects were masked by those of vibration either in the immediate period thereafter (changes in the latent period and duration of the aftereffect) or throughout the experiment until the animals died (changes in background intensity of the muscle bio-currents). Sometimes the results of the combined action seemed to be an algebraic summation of the results of the isolated action of the two agents (electric activity of the vestibular-tonic reaction and its aftereffect). In these cases vibration created the semblance of well-being, for the changes remained virtually within normal limits until the animals died. /101

Can vibration actually improve the condition of an irradiated animal and mitigate the effects of acute radiation sickness? Our data do not enable us to give a definite answer to this question. We also failed to find any pertinent information in the literature.

Conclusions

1. The combined action of double applications of vibration and γ -irradiation with a dose of 500 r increases the spontaneous electric activity of muscles in the hind leg of guinea pigs in a state of relative rest.
2. The electric activity of these muscles during and in the aftereffect of the reaction to adequate stimulation of the vestibular apparatus after the combined action does not change significantly (as compared with the control).
3. The latent period of the myoelectric reaction to vestibular stimulation increases after the combined action only shortly before the animals die.
4. The duration of the aftereffect of this reaction following the combined action of vibration and irradiation increases the first 5 days, but then sharply decreases.
5. In the case of the combined action of vibration and acute irradiation, vibration always significantly changes the radiation effects.
6. There are no statistically significant differences between the effects of the combined action of irradiation and vibration and those of irradiation alone, as far as the composition of the peripheral blood, weight, general clinical condition and survival time of the animals are concerned.

EFFECT OF ACUTE WHOLE-BODY γ -IRRADIATION ON EXCITABILITY
OF THE SPINAL REFLEX ARC

M. A. Kuznetsova

ABSTRACT

Total γ -irradiation with 500 r caused an increase of the latent period of motor defense reflexes in guinea pig extremities. At the same time, normal relation between stimulation intensity and the strength of response was preserved. The excitability threshold of the reaction increased in one group of the animals after irradiation, and decreased in the other group, but these changes were not statistically significant. Correlation between the dynamics of changes in excitability thresholds and of latency was not observed.

This article contains additional materials dealing with investigations on the effect of ionizing radiation on the functional state of the spinal reflex arc.

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Method

The experimental animals were 13 male guinea pigs weighing 350-500 g. One group was exposed to single whole-body irradiation with 500 r of Co^{60} at a rate of 261 r/min. The other group served as control. The threshold of excitability and latent period of the unconditioned defense flexor reflex were selected as the indices of spinal reflex arc function. The latent period was recorded accurate to 0.5 msec by our method (Kuznetsova, 1961) as modified by V. P. Godin and S. I. Gorshkov (1958).

The guinea pigs were placed in a chamber with a movable cover held tightly to the animals' back. When the cover moved, the mercury contact was broken, thus interrupting the circuit of the current fed to counters. The latent period was determined from the number of impulses supplied by a ZG-2 generator and recorded by scalars in the interval between the application of pain and the first slight twitching of the animal. In other respects, the method was the same as that described earlier (Kuznetsova, 1961). Painful electrocutaneous stimulation of the hind leg was achieved with plate electrodes.

A stimulating electrode 2.5 mm^2 in size was attached to the lower part of the shinbone while an indifferent electrode 16.5 mm^2 in size was placed on the belly. An ac current from a tone generator with a frequency of 100 /104 cps in three gradations was used as the stimulus.

1. The stimulus of constant physiological intensity was always equal to three times the threshold value.

2. The physically constant stimulus of moderate intensity was equal under normal circumstances to the threshold value multiplied by 6.

3. The physically constant stimulus of great intensity was more or less equal under normal circumstances to the threshold value multiplied by 10. The duration of the stimulating impulse was ~ 0.03 sec in all cases.

The design of the experiment was as follows:

(1) determination of the threshold and establishment of the value of the reflex of constant physiological intensity;

(2) determination of the latent period of the reflex to the physiologically constant stimulus (3 measurements);

(3) second determination of the threshold;

(4) determination of the latent period of the reflex to the physically constant stimulus of moderate intensity (3 measurements);

(5) determination of the latent period of the reflex to the physically constant stimulus of great intensity (2 measurements).

After the limits of fluctuations in the latent period of the reflex were established under normal conditions over a period of 1-2 weeks (3-4 experiments), the animals were irradiated and examined 1, 2, 3, 5, 7, 10, 12 and 15 days later.

At the same time that we investigated the parameters, we checked the peripheral blood, weight, temperature and clinical condition of the animals. To facilitate a comparison of the results obtained in the groups of animals with a different level and variability of the parameters under study, each absolute value measured after the action was expressed as a percentage of the deviation from the mean original value of this parameter. The percentage deviation was divided by the mean group spread of these values before the actions. The results were statistically processed by the median and χ -square criteria.

Results

The data obtained from the control throughout the observation period are presented in figures 1 and 2.

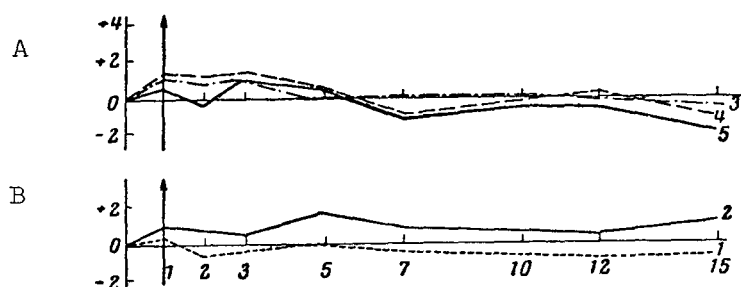


Figure 1. Changes in value of latent period of flexor reflex (A) and intensity of threshold stimulus (B) in control animals.

1--intensity of threshold stimulus in animals with exception of guinea pigs Nos. 62 and 69; 2--in entire group; 3-- duration of latent period of the reaction to weak physiologically constant stimulus; 4--to moderate and 5--to strong physiologically constant stimuli.

Abscissas--time in days; ordinates: top--duration of latent period in relative units; bottom--intensity of threshold stimulus in relative units. Arrow designates day when experimental animals were irradiated.

Analysis of the results shows that most control animals displayed no marked deviations of the threshold of excitability from the original level (fig. 1; 1). A sharp increase in the intensity of the threshold stimulus was observed in only two animals (fig. 2; 5 and 6). The mean changes in latent period of the reactions to the physically constant stimuli were mainly within the mean group deviation (fig. 1; 4 and 5). In the case of the marked deviations of the value of the latent period from the original background, no connection was discovered between them and the changes in threshold of excitability (fig. 2; 7, 7', 8 and 8'). In the animals with a sharp rise in the threshold of excitability, the latent period of the reaction to the strong stimulus not only did not lengthen, but it even fell below the original level (fig. 2; 6 and 6'). However, there was marked lengthening of the latent period in the reaction of the same animals to the stimulus of moderate intensity. Here also it was not caused by a drastic change in the threshold of excitability, as confirmed by the resemblance between these changes and the changes in value of the latent period of the reaction to the physiologically constant stimulus (fig. 2; 1, 3 and 5). /106

Thus, even significant changes in threshold of excitability in the control animals were not a decisive factor in changing the latent period of the reaction to the stimuli that we applied. The changes in threshold of excitability became of some significance only in cases where the physically constant stimulus under normal conditions was similar in intensity to the weak physiologically constant stimulus (fig. 2; 2).

The latent period of the reaction to the weak physiologically constant stimulus also failed to change significantly in most of the animals (fig. 1; 3),

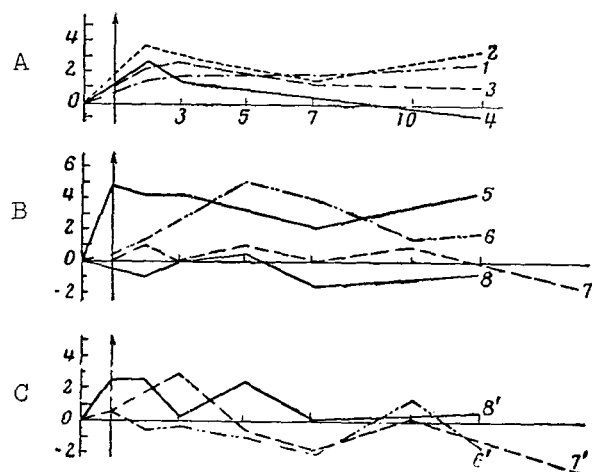


Figure 2. Relationship between changes in value of threshold sensitivity and in duration of latent period of flexor reflex in control animals.

A--duration of latent period in guinea pig No. 69 in reactions: 1--to physiologically constant stimulus; 2--to the weak stimulus, normally equal to 3 thresholds; 3--to moderate; 4--to strong physically constant stimulus.

B--intensity of threshold stimulus: 5--in guinea pig No. 69; 6-- in guinea pig No. 62; 7--in guinea pig No. 60; 8-- in guinea pig No. 71.

C--duration of latent period in reactions of: 6'--guinea pig No. 62 to strong physically constant stimulus; 7'-- guinea pig No. 60 to moderate physically constant stimulus; 8'--guinea pig No. 71 to moderate physically constant stimulus.

Abscissas--time in days; ordinates: A and C--latent period in relative units; B--intensity of threshold stimulation in relative units. Arrows designate days on which experimental animals were irradiated.

and only in two animals did this parameter rise slightly above the original level (fig. 2; 1). As for the reactions to all three stimuli, there was a tendency for the latent period to contract in the course of work (phenomenon of familiarization). This tendency was more pronounced for the strong stimulus than it was for the other two stimuli. Analysis of the experiments with impairment of the correct intensity relations between the reactions to the strong and weak stimuli¹ showed that in the course of work the intensity /107 relations stabilized and improved (fig. 3).

¹In almost all experiments the physiologically constant stimulus was weaker than the physically constant stimulus. The rare instances in which the difference between the values of these stimuli leveled out after a sharp rise in the threshold were ignored in processing the material.

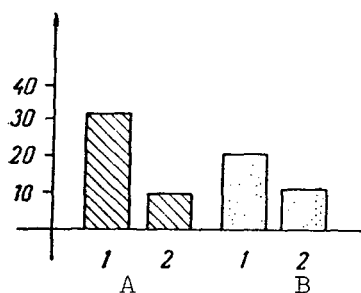


Figure 3. Disturbance of force relationships on irradiated and nonirradiated animals (quantity of tests shown in percent).

A--control; B--experimental groups of animals.

In experimental group: 1--before action; 2--after irradiation; in control (1 and 2) the investigation took place in the same period as in the experimental group.

Thus, although the duration of the latent period of the reactions to the three stimuli also differed somewhat from the original background, the changes were slight and for all the stimuli varied within narrow limits. Statistical processing confirmed the lack of significant changes in the reactions to all three stimuli by the control animals during the observation period.

Figures 4 and 5 show the changes in intensity of the threshold stimulus in the irradiated animals. The curves indicate that irradiation caused definite changes in the thresholds of excitability, although these changes were not 108 statistically significant.

The experimental animals were divided into two more or less equal groups according to the nature of the reaction. One group (4 guinea pigs), starting the 3rd to 5th days after the action, exhibited a gradual lowering of excitability with a sharp decrease in individual animals just before death (fig. 4A). The other group, however, showed a decrease in the value of the threshold stimulus after irradiation (fig. 4B). The sharpest drop in the threshold of excitation, starting the first day after the action, was noted in guinea pig No. 65, the only animal to survive the exposure. The threshold of excitability remained at this low level for a week and then gradually returned to normal.

The threshold of excitability in this group of animals did not always rise in the predeath period. For example, guinea pig No. 64 died with low values of the threshold stimulus.

As in the control animals, the changes in threshold of excitability generally were not correlated with the changes in duration of the latent period following the physically constant stimuli. Even when the value of the threshold stimulus increased sharply in the predeath period, the duration of the latent period that followed the physically constant stimuli tended to fluctuate within normal limits (fig. 5).

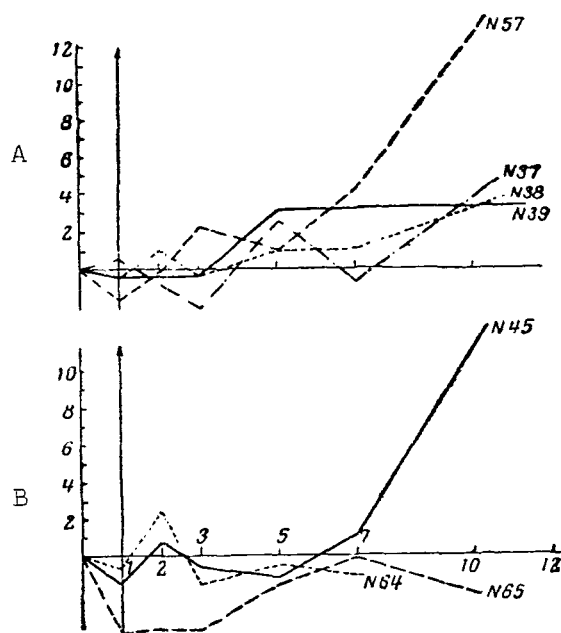


Figure 4. Individual changes in threshold of excitability of animals after irradiation. A--rise in threshold of excitability; B--lowering of threshold of excitability of motor defense reflex. Number of guinea pigs is indicated on curves. Abscissas--time in days; ordinates--changes in intensity of threshold stimulus in relative units. Arrow designates day of irradiation.

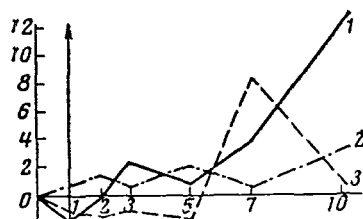


Figure 5. Relationship between changes in value of threshold stimulus and changes in value of latent period of flexor reflex in guinea pig No. 57. 1--value of threshold stimulus; duration of latent period of flexor reflex; 2--to moderate; 3--to strong physically constant stimulus. Abscissa--time in days; ordinate--relative values of threshold stimulus and latent period. Arrow designates day of irradiation.

Irradiation caused marked changes in duration of the latent period of the reaction to all three types of stimulation as compared with both the original background and the control animals. The differences from the control were statistically significant in all cases. There were two kinds of changes. Some were wavelike in character, thus tending to produce an overly long latent period in the middle (or at the beginning) of the investigation and just before death (fig. 5; 3; fig. 6; 5); or the value of this parameter throughout the investigation remained at a high level, although the original level was sometimes restored just before death (fig. 6; 4).

The individual as well as composite curves for the entire group of experimental animals (fig. 6; 1-3) indicate that the single whole-body /109

exposure to the γ -rays of Co^{60} (500 r) considerably lengthened the latent period of the reactions to all three stimuli, compared to the original background and control group. The least change was noted in the reaction to the strong stimulus (fig. 6; 3); the greatest change in the reaction to the weak stimulus (fig. 6; 1). The reaction to the moderate stimulus occupied an intermediate position (fig. 6; 2). All this suggests that impairment of the excitability of

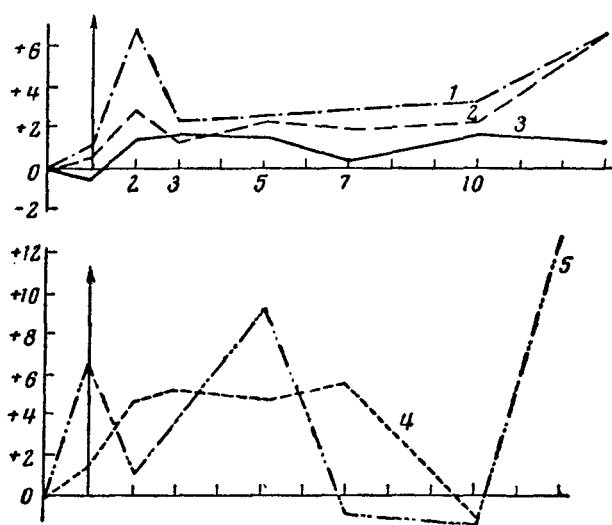


Figure 6. Changes in duration of latent period of flexor reflex in irradiated animals.

Mean duration of the latent period of the reaction to: 1--weak physiologically constant stimulus; 2--moderate physically constant stimulus; 3--strong physically constant stimulus.

Individual changes in duration of latent period of reaction to moderate physically constant stimulus: 4--in guinea pig No. 38; 5--in guinea pig No. 39.

Abscissas--time in days; ordinates--latent period of reflex in relative units. Arrows designate days of irradiation.

the nervous system is of the narcotic phase type. Therefore, the number of experiments with disrupted intensity relations in the group of irradiated animals decreased, as was the case with the control group (fig. 3).

Discussion

There are now fairly numerous references in the literature to the fact that irradiation brings about marked changes in reflex excitability of the various divisions of the central nervous system (Lebedinskiy and Nakhil'nitskaya, 1960; Livshits, 1961). As a rule, it lowers reflex excitability by raising the threshold of excitability, lengthening the latent period of the response, suppressing bioelectric activity and impairing conditioned activity. The suppression stage is often preceded by an usually brief period of increased excitability. /110

Similar results were obtained in an investigation of spinal reflex activity. N. K. Poplavskiy (1956) observed phasic changes in excitability of the general motor reaction to pain in mice exposed to whole-body X-irradiation with doses of 360-1440 r. Excitability increased during the first 2 hours, then returned to normal and sharply decreased before death. A similar decrease in excitability of the defense reflex preceded by a brief (during the first 24 hours) increase was also noted by S. A. Davydova (1958) after she X-irradiated dogs with 500-600 r. The phase of increased excitability was longer in the surviving animals. It lasted about 3-5 days, then the threshold of excitability returned to normal.

In our investigations, changes in excitability were not the same in all the animals exposed to 500 r of γ -rays from Co^{60} ; in fact, they sometimes proceeded in opposite directions. In some of the animals, they resembled the described changes and were reflected in a gradual lowering of excitability with a sharp drop in the predeath period. A slight increase was noted in a few animals between the 1st and 3rd days (fig. 4A). The reaction of the other animals was more like the changes observed by Davydova in surviving dogs. These guinea pigs exhibited only an increase in excitability, which before death either decreased sharply or remained at the original level. The surviving animal showed the longest and most distinct increase in excitability. The intensity of the threshold stimulus did not return to normal without a preliminary increase until the 10th day. The changes that we observed in the duration of the latent period of the defense flexor reflex are completely consistent both with the literature (Davydova, 1958; Gvozdkova, 1957, 1962; Kudritskiy, 1955, 1957; Fedorova, /111 1957) and with the results of our experiments on rabbits (Kuznetsova, 1961). X-irradiation with a dose of 400 r likewise markedly lengthened the latent period and it remained at a high level for 40 days.

The appearance of phasic states in the excitability of the nervous system as a result of ionizing radiation has been noted by many authors, who mostly investigated, however, cortical function (Nemenov, 1932; Livshits, 1954; Meyzerov, 1959; Kurtsin, 1958a; Samoylova, 1959; and others). It was only in Davydova's work (1958) that we found references to phasic states arising in the spinal

reflex arc after irradiation. The author notes that paradoxical phases appeared and became accelerated in dogs irradiated with 500, 600 and 800 r. In our experiments, the changes in excitability of the spinal reflex arc were of the narcotic phase type without any disruption of the intensity relations.

Ionizing radiation is known to cause marked changes in all the links of the motor reflex arc (Lebedinskiy and Nakhil'nitskaya, 1960). Therefore, the duration of the latent period tends to vary with impairment of the functional state of each of these links. In addition, one cannot ignore the part played by functional impairment of the midbrain and medulla oblongata in the origin of changes in the characteristics of the spinal reflexes (Gvozdikova, 1961).

However, it would seem that the changes observed after irradiation in the duration of the latent period should be linked to the disturbances developing in the central link of the motor reflex arc. This is confirmed by O. S. Il'ina's data (1956), derived from experiments on frogs, and by the electrophysiological investigations of Z. M. Gvozdikova (1957) and S. A. Davydova (1958).

The fact that the changes in duration of the latent period that we observed were not correlated with the changes in threshold of excitability provide further confirmation of our hypothesis. A. F. Lebedinskiy and Z. I. Nakhil'nitskaya (1960) conjecture that the disruption of reflex activity in irradiated animals is due primarily to changes in the synaptic formations of the central portion of the reflex arc.

Conclusions

1. Whole-body γ -irradiation with 500 r of Co^{60} caused regular changes in the threshold of excitability and duration of the defense flexor reflex in guinea pigs. The changes in the threshold of excitability were not statistically significant; however, those in the duration of the latent period were significant. /112

2. The latent period of the reaction to the three kinds of stimuli of varying intensity that were used indicated that the changes in reflex excitability of the spinal reflex arc were of the narcotic phase type.

3. The changes in duration of the latent period were correlated with changes in the threshold of excitability. It is fair to assume that these parameters reflect functional changes in different parts of the reflex arc.

EFFECT OF GENERAL VERTICAL VIBRATION ON SPINAL REFLEX ARC FUNCTION

M. A. Kuznetsova

ABSTRACT

Total vertical vibration of 70 cps, amplitude 0.4 mm and duration of 15 min was applied twice with a 24-hour interval between exposures. It caused, not sharp, but statistically significant increase of the excitability threshold of motor defense reflex in guinea pig extremities.

The latency in one group of the animals increased and in the other group decreased. In all animals, responses to stimulators of weak and high intensity were equalized. This fact indicates development of parabiologic phenomena in the investigated reflex arc.

Great demands are made on the motor apparatus during space flight. Hence, a study of the effect of vibration on motor activity is a subject of considerable interest. /113

The purpose of this investigation was to analyze the effect of vertical vibration on the functional state of the unconditioned defense flexor reflex arc.

Method

The experimental animals were 14 male guinea pigs weighing 350-500 g. One group was exposed to vibration twice, with an interval of 24 hours between exposures. The rest of the animals served as the control.

Vertical vibration was applied with a frequency of 70 cps, amplitude of 0.4 mm, 15 min duration.

The thresholds of excitability and latent period of the defense flexor reflex were used as indices of the functional state of the arc. The recording method, design of the experiment and method of processing the data are described in the preceding article.

Besides investigating the above-mentioned parameters, we observed the peripheral blood, weight, temperature, and clinical condition of the animals.

Results

The animals exposed to vibration twice exhibited distinct but similar changes in the thresholds of excitability as reflected in a slight increase in intensity of threshold stimulation (fig. 1). The differences from the control animals were statistically significant. The changes in thresholds of excitability, as in the control group, were not correlated with changes in the latent period. This is evident from figure 2, which shows individual curves of changes in threshold of excitability and latent period. In guinea pig No. 56, the latent periods of the reactions to the moderate and strong physically constant stimuli were shortened by vibration, while the threshold of excitability rose (fig. 2; 2, 4 and 4'). In guinea pig No. 68, although both parameters increased, they did not change in parallel (fig. 2; 1, 3 and 3'). The latent period of the reaction to the strong stimulus increased sharply between the 10th and 12th days after vibration, but the intensity of the threshold stimulus at this time decreased slightly. The latent period of the reaction to the strong stimulus changed more drastically than did the latent period of the reaction to the stimulus of moderate intensity. Yet the latter should have been more dependent on changes in the value of the threshold, if the changes in these parameters were interrelated.

Vibration produced weak changes in the thresholds of excitability. But the changes in the latent period were sharp. The differences from the controls¹

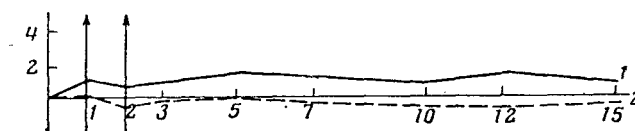


Figure 1. Changes in mean value of the threshold stimulus in animals subjected to vibration twice.

1--mean value of threshold stimulus in group of animals subjected to vibration twice; 2--same in control group. Abscissa--time in days after action; ordinate--intensity of threshold stimulus expressed in deviations from mean value of original background taken as 100 percent and related to mean group deviation under normal conditions. Arrows designate day of vibration.

¹The changes in duration of the latent period of the flexor reflex in the control are shown in figure 1 of the article in this collection preceding this one.

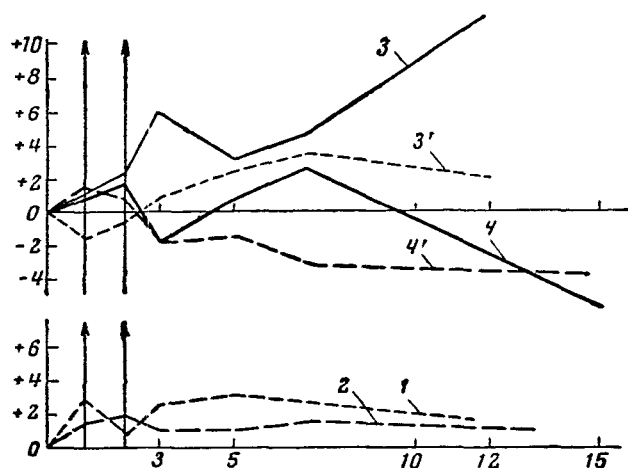


Figure 2. Relationship between changes in value of threshold stimulus and changes in duration of latent period of flexor reflex in group of animals subjected to vibration twice.

Value of the threshold stimulus: 1--in guinea pig No. 68; 2--in guinea pig No. 56. Duration of latent period: in guinea pig No. 68: 3--in reactions to strong, 3'--in reactions to moderate physically constant stimuli; in guinea pig No. 56: 4--in reactions to strong, 4'--in reactions to moderate physically constant stimuli.

Abscissas--time in days; ordinates: top--latent period, bottom--intensity of threshold stimulus. Arrows--same as in figure 1.

in the reactions to all three types of stimulation were likewise statistically significant.

The animals were divided into four groups according to the latent period of the reactions.

In the first group (guinea pigs Nos. 40, 41 and 63, fig. 3A), the latent period of the reaction to the weak stimulus lengthened only during the first three days after vibration. These changes were about equal in intensity to the changes in the latent period of the reaction to the strong stimulus. But the changes in the reaction to the stimulus of moderate intensity were much less significant. Consequently, at this time the animals in this group exhibited a lowering of reflex excitability with a tendency toward impairment of the intensity relations of the phase of moderate stimulation type.

Starting the 5th day, the values of the latent period of the reactions to the stimuli of low and moderate intensity were almost normal (the fluctuations in the value of this parameter were within the mean group deviation from the norm). However, the value of the latent period of the reaction to the strong

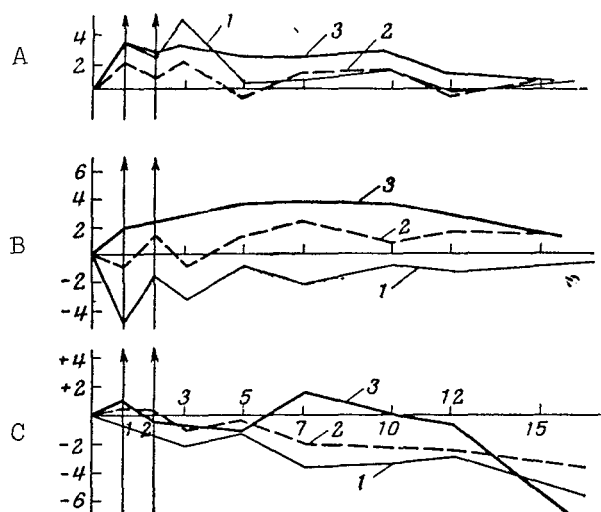


Figure 3. Changes in mean duration of latent period of flexor reflex after two exposures to vibration.

A, B and C--mean duration of latent period by groups of experimental animals in reactions to: 1--weak physiologically constant stimuli; 2--moderate; 3--strong physically constant stimuli. Ordinate--duration of latent period in relative units. Abscissa and arrows--same as in figure 1.

stimulus remained until the 10th day of the experiment at the same high level as on the 3rd day after the application of vibration.

Thus, the changes in reflex excitability of the investigated nerve arc during the second part of the experiment reflected a tendency toward disruption of the intensity relations of the balanced phase type at a low level.

In the animals of the second group (guinea pigs Nos. 61 and 68, fig. 3B), the latent period of the reaction to the stimulus of moderate intensity shortened, while that of the reaction to the strong stimulus lengthened. The latent period of the reaction to the stimulus of moderate intensity also lengthened, but only slightly.

These changes in the values of the latent period were traced throughout the experiment. Thus, there was a prolonged impairment of reflex excitability in response to vibration by these animals along with a tendency to disruption of the intensity relations of the balanced phase type at a medium level. /117 This tendency was somewhat more pronounced during the first three days after exposure to vibration, when the reaction to the stimulus of moderate intensity was still virtually unchanged.

In the animals of the third group (guinea pigs Nos. 56 and 72, fig. 3C), as in the animals of the preceding group, the latent period of the reaction to

the weak stimulus shortened. The changes were more pronounced during the second part of the investigation. The changes in reactions to the stimuli of great and moderate intensity during the first 5 days after vibration were about the same and were also reflected in a shortening of the latent period. However, these changes were slight and much less pronounced than were the changes in reaction to the weak stimulus. Starting with the 7th day, the duration of the latent period of the reaction to the strong stimulus returned to normal, but that of the reactions to the moderate and strong stimuli shortened even more than in the first period.

Thus, in this group of animals vibration produced a persistent increase in reflex excitability of the nerve arc under investigation with a tendency toward disruption of the intensity relations of the balanced phase type on a high level. This tendency was most evident in the second period of the investigation. Guinea pig No. 55 (fig. 4) was an exception (4th group) and its reaction will be examined a little later.

This analysis of the results shows that there was a marked and prolonged shortening of the duration of the latent period of the reaction to the weak stimulus in half of the animals (Nos. 56, 61, 68 and 72) from the very first day of exposure to vibration. The other animals (Nos. 40, 41, 63 and 55) reacted during the first 5 days mainly with a lengthening of the latent period which, beginning the 6th or 7th day, returned to normal or was sharply reduced.

As we mentioned before, all measured values of the latent periods were expressed in the form of a percentage deviation from the mean value of this parameter before exposure.

This explains why the median of all the values before exposure was zero (the number of positive and negative deviations from the mean norm could only be the same). After vibration the general median of the deviations of the value of the latent period of the reactions to the weak stimulus from the mean norm for all experimental animals shifted slightly toward the negative deviations and became -0.58. Consequently, the tendency toward a shortening of the latent period as compared with the original level predominated in the reactions to the weak stimulus.

However, in the reactions to the strong stimulus, there was a tendency /118 for the latent period to lengthen.

First, almost all animals after vibration exhibited either a persistent lengthening of the latent period (fig. 3A; 3 and B; 3) or a tendency for it to lengthen, as compared with the original value in the reaction to the weak stimulus (fig. 3C; 3). Only one animal (guinea pig No. 55) reacted to vibration with a shortening of the latent period of the response to the strong stimulus (fig. 4; 3), whereas during the first 5 days of the investigation the latent period of its response to the weak stimulus was high (fig. 4; 1). Second, in the animals that exhibited a lengthening of the latent period after vibration, changes in the reaction to the strong stimulus were sharper than those in the reaction to the weak stimulus. The latent period of these reflexes remained long throughout the investigation, and changes in it were of the same magnitude as those following the reaction to the weak stimulus.

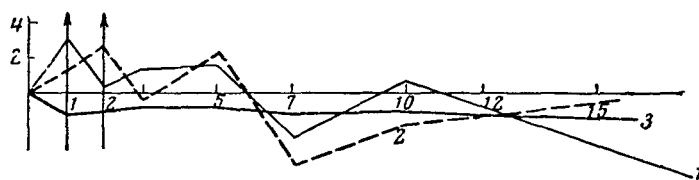


Figure 4. Changes in duration of latent period of flexor reflex in guinea pig No. 55. Symbols same as in figure 3.

As a result, the median of the deviations of the latent period of the reaction to the strong stimulus from the mean value of this index before exposure rose from zero to +1.3.

As for the reaction to the stimulus of moderate intensity, here also there was a tendency for the latent period to lengthen, although this tendency was less pronounced than in the case of the reaction to the strong stimulus. Of the 8 animals subjected to vibration, only 2 reacted with a shortening of the latent period (fig. 3C; 2). In the other animals, the changes in duration of the latent period throughout most of the investigation lay in the region of the positive deviations (fig. 3A; 2 and B; 2). Consequently, the median of the deviations of the latent period of the reaction to the moderate stimulus from the mean value of this index before exposure rose from zero to +0.96.

However, the increase in latent period of the reaction to the stimulus of moderate intensity was very slight and invariably much smaller than in /119 the reaction to the strong stimulus.

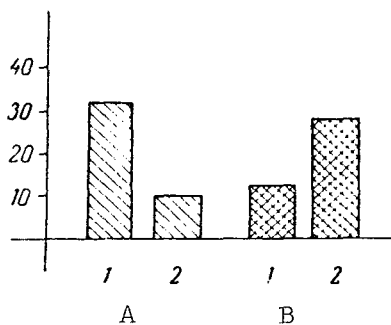


Figure 5. Disruption of intensity relations in animals investigated. A--control group; B--experimental group; in the experimental group: 1--before vibration; 2--after vibration; in the control (1 and 2) investigation took place at same time as in experimental group. Ordinate--number of experiments (%) with disruption of intensity relations.

Thus, as the intensity of the stimulus was reduced, the tendency for the latent period to shorten grew, and vice versa. Meanwhile the change in intensity relations was of the balanced phase type.

Increasing disruption of the intensity relations in the vibrated animals is also shown in figure 5. Whereas these relations in the control group stabilized and improved in the course of the investigation, in the experimental group the number of experiments with disrupted intensity relations grew, although the differences in the data were not statistically significant.

The vibrated animals did not differ significantly from the controls in weight, temperature, peripheral blood or clinical symptoms.

Discussion

There are conflicting reports in the literature on the change in excitability in the various divisions of the central nervous system under the influence of vibration. Some authors observed the onset of excitation (Don-skaya and Stoma, 1960); others, the development of inhibition with a tendency toward broad irradiation (Butkovskaya, 1957). Instances of disruption of the relations between the main nervous processes (Mikheyeva, 1950), phenomena of weakened internal inhibition (Andrianov, 1959) and growth in number of errors in complex psychomotor problems (Catterson et al., 1962) have been observed. Some authors note the existence of a relationship between the reaction of the nervous system, its original functional state, and type of higher nervous activity (Skachedub, 1957; Sircina and Kharicheva, 1959; Usenko, 1961).

Analysis of the results of our experiments shows that the reaction of the nervous system to vibration varied with original functional state /120 and the characteristics of the nervous system of the individual animals. These characteristics may well have been due to the type of higher nervous activity, but we have no relevant experimental data to confirm this. Reflex excitability and conduction changed in diametrically opposite directions among the different animals. Some exhibited a sharp and persistent increase in reflex excitability along with a tendency toward disruption of intensity relations of the balanced phase type at a high level (third group of vibrated animals) and phasic states (second group of vibrated animals) at a medium level.

Other animals (first group) reacted during the first 5 days with a sharp decrease in reflex excitability and conduction. The change in intensity relations was of the moderate stimulus phase type. This phenomenon, a special case of the balanced phase, is quite rare (Rikman, 1928; Rozental', 1936; Makarov, 1940). Seven days after exposure, this group of animals exhibited a disruption of intensity relations of the balanced phase type at a low level.

These disruptions of intensity relations suggest that vibration gives rise to the development of parabiogenic phases in the reflex arc under study. Similar phases have been observed in the higher divisions of the CNS under the influence of a variety of physical and chemical agents.

A comparison of the effects of vibration with the data that we obtained on animals exposed to 500 r of γ -radiation, and with the material included in the preceding article of this collection, shows that the effect of two exposures to vibration on the latent period of the defense flexor reflex is equal to the effect of a lethal dose of radiation. The results of our experiments agree with the published data (Galat, 1960), showing that vibration causes protective inhibition to arise in the spinal reflex arc. The author found that even 5 min vibration, with a frequency of 30 cps and an amplitude of 2.5 mm, first caused the flexor reflex to disappear and then lengthened its latent period. These investigations are the only work on the effect of vibration on spinal reflexes that we were able to discover in the literature. Our finding that changes in duration of the latent period do not vary with changes in the threshold of sensitivity indicates that the changes produced by vibration in the spinal reflex arc, like those following irradiation and combined factors (examined in /121 other articles in this collection), reflect chiefly the changes that take place in the motor centers of the spinal cord.

Conclusions

1. Vertical vibration with a frequency of 70 cps and an amplitude of 0.4 mm applied to guinea pigs for 15 min produced during the next two days major, statistically significant changes in the functional state of the reflex arc of the defense flexor reflex. These changes lasted throughout the 12 days of the investigation.
2. These changes were reflected in a significant but gentle rise in the thresholds of excitability and in complex changes in the duration of the latent period of the reflex arc under study.
3. There was a tendency for the latent period of the reflexes to the weak stimulus to shorten and to lengthen after exposure to the moderate and strong stimuli. It was more pronounced in the case of the latter. The changes in latent period of the reaction to the stimulus of moderate intensity were invariably much smaller than that of the reaction to the strong stimulus. These phenomena were indicative of the onset of parabiosis in the reflex arc.
4. The changes in duration of the latent period of the reactions were not correlated with the changes in threshold of excitability.
5. The effect of two exposures to vibration on the duration of the latent period of the defense flexor reflex was equivalent to that of a lethal dose of radiation, as we described in the preceding article of this collection.

COMBINED EFFECTS OF VIBRATION AND IONIZING RADIATION ON THE FUNCTIONAL STATE OF THE SPINAL REFLEX ARC

M. A. Kuznetsova

ABSTRACT

The complex effect of total vertical vibration and 500 r γ -irradiation on the excitability threshold and the latency of motor defense reflex in guinea pig hind extremities were studied. Total vertical vibration of 70 cps, 0.4 mm amplitude and 15 min duration was applied twice: 30-40 min before and 24 hours after irradiation. In response to complex action of these factors, some properties of separate effects of each factor were combined. In one part of the animals vibration effects predominated, while in the other part irradiation prevailed.

According to the reactions of some functions, the results of the complex effect took an intermediate position between vibration and radiation effects.

The purpose of our work was to investigate the combined effects of vibration and radiation on the functional state of the defense flexor reflex arc. /122

Method

The experimental animals were 11 male guinea pigs weighing 350-500 g. One group was subjected to vibration twice: 30-40 min before and 24 hours after irradiation. The physical conditions of the irradiation and vibration were the same as in the investigations of the isolated effects of each of the factors (compare preceding articles in this collection). The remaining animals were subjected to neither factor and served as the control. As in the preceding investigations, the threshold of excitability and latent period of the defense reflex of the hind leg were chosen as indices of the spinal reflex arc function.

Besides investigating these parameters, we also observed the peripheral blood, weight, temperature and clinical condition of the animals. The recording of the indices, design of the experiment, method of processing the data and graphic representation of the results are described in the earlier articles.

Results and Discussion

The results of the combined action of vibration and irradiation on the threshold of excitability of the unconditioned flexor reflex are shown in figure 1B. It is evident from the figure that the changes in threshold of excitability in this group of animals were quite clear-cut, although not statistically significant. These changes were qualitatively similar to those noted in the animals exposed to radiation alone. The combined action of irradiation and vibration, like that of irradiation alone, produced changes in the threshold of excitability in two opposite directions. In some animals, the intensity of the threshold stimulus grew from the first days after the action (fig. 1; 5), whereas in others, the intensity decreased (fig. 1; 6). A sharp rise in the threshold was noted in a few animals in this group just before death. /123

However, there was no correlation between the changes in threshold of excitability and duration of the latent period (fig. 1; 1, 2, 3 and 4). Figure 1 shows that in guinea pig No. 59, the lengthening of the latent period of the reflexes to the weak and strong stimuli between the first and fifth days after the action coincided in time with a rise in the threshold of excitability. On the seventh day the latent periods of the reflexes to these stimuli decreased sharply, whereas the threshold rose even more. /124

The combined action of vibration and irradiation brought about certain changes in duration of the latent period that differed significantly from the original background and the control. It is interesting to note that the animals exposed to the combined action exhibited both the characteristics of the reaction to vibration and the characteristics of the reaction to irradiation. The influence of irradiation predominated in some cases; that of vibration, in others.

Thus, the animals in this group could be divided into two parts. One closely resembled the irradiated animals in regard to the correlation of effects in the reactions to the weak and strong stimuli. As in the animals exposed to irradiation alone, changes in excitability of the nervous system were of the narcotic phase type. The lengthening of the latent period of the reaction to the weak stimulus was more marked than that of the reaction to the strong stimulus, while the lengthening of the latent period of the reaction to the moderate stimulus occupied an intermediate position, resulting in preservation of the correct intensity relations between the reactions to the various stimuli (fig. 2, curve 1). /125

The only exception occurred on the 10th day when the latent period of the reaction to the strong stimulus increased sharply. The effect of vibration on this group of animals could be detected only in guinea pig No. 59, in which we were able to observe a moderate stimulus phase. In this animal, as in the guinea pigs exposed to vibration alone, the reflexes to the moderate stimulus were least affected. The changes in duration of the latent period of the reactions to the moderate stimulus were less pronounced than in the reactions to the strong and weak stimuli (fig. 1; 1, 2 and 3). The moderate stimulus phase was never detected in the animals exposed only to irradiation.

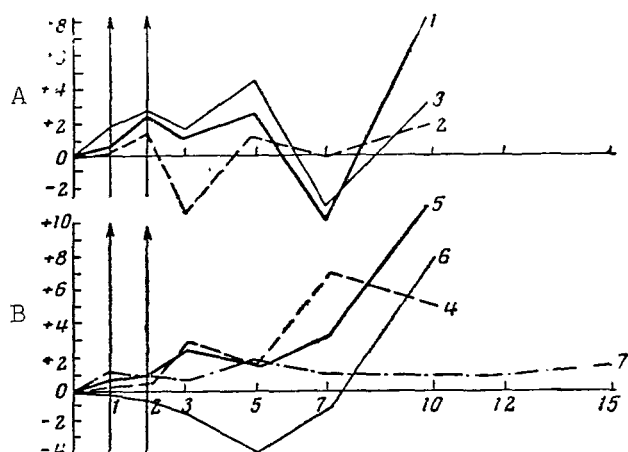


Figure 1. Changes in value of threshold stimulus and in latent period of defense flexor reflex in animals exposed to combined action of vibration and irradiation. A--individual data on change in duration of latent period in guinea pig No. 59 in its reactions to: 1--strong; 2--moderate; 3--weak stimulus; B--changes in value of threshold stimulus: 4--in guinea pig No. 59 (individual data); 5--mean data from the group of animals in which threshold of excitability rose after combined action; 6--mean data from group of animals in which threshold of excitability dropped in first phase following combined action; 7--mean data from control animals. Abscissas--time in days after action; ordinates--value of parameter expressed in relative units. Arrows designate days of action: left--combined action of γ -irradiation and vibration, right--vibration alone.

However, the changes in latent period in the other group of animals exposed to the combined action resembled the effects of vibration, although irradiation had some influence. The duration of the latent period of the reaction to the strong stimulus lengthened markedly from the very first days after the action and persisted at a fairly high level throughout the investigation (fig. 2B; 2). The combined action here did not differ significantly in intensity from the action of vibration. There was, as it were, an algebraic summation of the effects of irradiation and vibration in the reactions of these animals to the weak stimulus. As we saw before, the effects of vibration and irradiation on the reaction to the weak stimulus were directly opposite (after vibration there was a tendency for the latent period to shorten; after irradiation, to lengthen). The duration of the latent period remained unchanged in this group of animals.

Thus, the decrease in excitability of the reflex arc in these animals, as in the animals exposed to vibration, proceeded like the balanced phase type at a low level. The only difference was that this tendency was somewhat

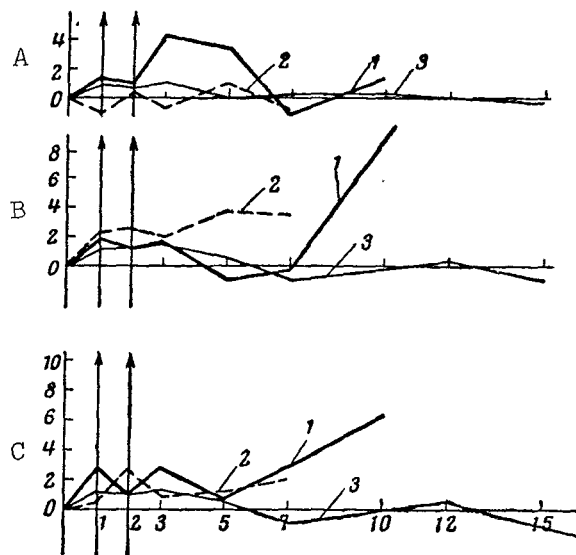


Figure 2. Changes in duration of latent period of flexor reflex in reactions to weak physiologically constant (A), strong (B) and moderate (C) physically constant stimuli. 1, 2--group of animals exposed to combined action; 3--control group. Ordinate--latent period in relative units. Other symbols same as in figure 1.

less pronounced after the combined action. Since the changes in reflex excitability in some animals resembled those in the irradiated animals, while in other animals they resembled the changes in the vibrated animals, the number of experiments with disruption of the intensity relations did not change (as compared with the normal state) for the group as a whole (fig. 3).

The changes in latent period of the reaction to the moderate stimulus likewise occupied an intermediate position between the changes in the irradiated animals and those in the vibrated animals. They were smaller than in the irradiated group but greater than in the vibrated group (fig. 4). /126

This analysis of the results reveals a complicated pattern. In some cases the effect of either of the factors predominated over that of the other. In other cases there was, so to speak, an algebraic summation.

No differences were noted between the animals subjected to the combined action and those exposed to irradiation alone, with respect to weight and peripheral blood. Our data do not provide a sufficient basis for evaluating the significance of the differences in survival rate of the animals in the two groups. We can only say that after the combined action death occurred one /127 or two days sooner than after irradiation alone. All animals subjected to the combined action died. One of the irradiated animals survived.

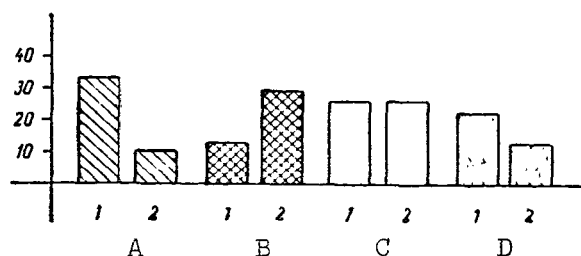


Figure 3. Disruption of intensity relations in animals exposed to combined and isolated action of vibration and irradiation.

A--control group; B--vibrated group; C--group subjected to combined action; D--irradiated group. 1--experiments with disruption of intensity relations under normal conditions; 2--experiments with disruption of intensity relations after exposure. Investigations of control (1 and 2) were conducted at same time as in experimental groups.

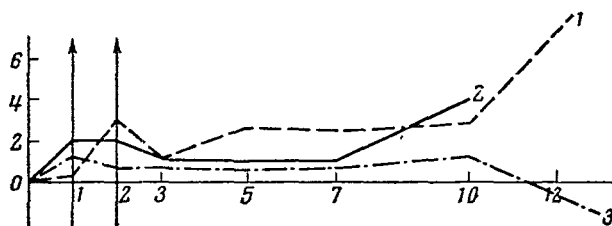


Figure 4. Changes in duration of latent period of flexor reflex in reaction to physically constant stimulus.

1--irradiated animals; 2--animals subjected to combined action of vibration and irradiation; 3--animals subjected to vibration alone. Other symbols same as in figure 2.

We were able to find only two references in the literature to the combined action of ionizing radiation and dynamic space flight factors. A. N. Ganshina (1961) noted that radiation lesions were intensified when irradiation was combined with vibration. Ivanov et al. (1962) showed that in animals exposed to irradiation, while rotated in a centrifuge, the effect of irradiation was weaker than in animals exposed under ordinary conditions. In the former, the weight loss was somewhat less severe and death tended to occur a little later. This indicates that not only vibration, but acceleration alters the reaction of the organism to irradiation, and that the additional action of mechanical factors may either weaken or intensify the radiation reactions.

Conclusions

1. The combined action of vibration and irradiation produced significant changes in the functional state of the defense flexor reflex arc. These changes included both the threshold of excitability and the duration of the latent period of the reflex. Parabirotic phases were noted in some of the reactions to the various stimuli.

2. The duration of the latent period and the threshold of excitability changed independently of one another.

3. A complex interaction of the effects of irradiation and vibration occurred after the combined action:

(a) the effect of one of the two agents predominated, or

(b) there was a peculiar algebraic summation of the effects of the two agents.

EFFECT OF GENERAL REPEATED VIBRATION ON OXYGEN
TENSION IN THE BRAIN OF RATS

L. D. Luk'yanova

ABSTRACT

Single vibration of animals (70 cps) caused the appearance of 3 successively developing phases: (a) increase of oxygen consumption by cerebral tissue, (b) decrease of its consumption, (c) restoration period. Repeated vibrations strengthened the changes in each phase. Adaptation phenomenon was not observed. Changes in the level of oxidative processes induced by vibration are not identical in different parts of the brain. Vibration causes the decrease of lymphocytes during the first hour, followed by leukocytosis.

The study shows that the changes in oxygen tension and in the level of its consumption by cerebral tissue reflect a specific state of nerve tissue, that develops in response to vibration effect.

In view of the important role played by the brain in the activity of /128 higher organisms, it is easy to understand why there is great interest in possible changes in its metabolism under the conditions of space flight, specifically, the physicochemical alterations in brain cells brought about by respiration.

The brain at rest seems to obtain most of its energy aerobically. Oxygen is consumed in the brain much more rapidly than in other tissues, averaging 3.5 ml per 100 g of tissue per minute in a healthy person. For a human brain of average weight it amounts to a total oxygen consumption of about 50 ml/min, or 20 percent of the oxygen consumed by the body as a whole. The rate is 20 times more intense than in the muscles.

The continuous supply of oxygen to the brain is essential for its normal activity. Even a short interruption may sharply impair nervous activity.

The increased demands made on the brain during space flight require very careful attention to the normal oxygen supply of the body and to the oxidative processes that take place at this time in brain tissue proper. A well known factor in space flight is vertical vibration. Relevant investigations have shown that intense vibration causes changes in the central nervous and cardiovascular systems and impairs neurotrophic regulation. Hence vibration

can be assumed to exert some influence on the oxidative processes in brain tissue, particularly on its consumption of oxygen.

Method

It is now possible to determine the oxygen concentration of the brain /129 in multiple experiments by using the "oxygen cathode" method, which is based on the principle of polarographic analysis (Davies and Brink, 1942). When negative voltage of about 0.4-0.8 V is supplied to the cathode (platinum electrode), electrolytic reduction of oxygen takes place in the solution, creating a current proportional to the oxygen concentration. Any nonpolarizable electrode may be used as the anode. In living systems it is best to use a silver-chlorinated silver electrode (Ag - AgCl).

The speed of the reaction is limited by the energy barrier of the reduction process and by the rate at which oxygen reaches the cathode. This varies with the concentration gradient on the electrode surface.

We can select, therefore, conditions whereby oxygen reaches the electrode surface at a maximum speed for the given diffusion conditions, and the electrolysis current (critical diffusion current - I_{cr}) changes very little, being virtually independent of changes in potential of the circuit. In the present investigation this was accomplished by supplying voltage (0.6 V) to the cathode. Thus, I_{cr} characterizes oxygen tension (pO_2) in the tissues under study (in discussing the results, both values will be treated as equal).

Since the solubility of oxygen in an aqueous solution is very low, the oxygen concentration at constant temperature and under ordinary pressure is proportional to the "oxygen tension" in the solution, to its partial pressure (pO_2) or amount of oxygen present in equilibrium with the gaseous medium.

Electrochemical and mathematical analysis of the "oxygen cathode" method (Kolthoff and Lingane, 1946) shows that it can now be effectively used in experiments on animals.

We used as the cathode a platinum electrode of the open disk type, a platinum wire 0.1 mm in diameter with an uninsulated pointed tip covered with collodion. Before insertion into the brain, the electrodes were calibrated under standard conditions (physiological solution at a constant temperature and pressure). The nonpolarizable electrode in the form of a chlorinated

silver plate 25 mm² in size was sewed to the muscles of the back while the deriving tip was drawn to the outside. The line diagram was the same as that used by A. D. Snezhko (1956). As recording devices we employed automatic

recorders ($H = 373/2$) with a maximum sensitivity of $0.5 \cdot 10^{-6}$ a (reading /130 accurate to 10^{-8} a).

This made it possible to have continuous tracings on graph paper. Compensation devices were hooked up to the automatic recorders to permit observation of slight changes in the signal with heavy current on the most sensitive scales.

An ac amplifier was attached to measure low currents of the order of 10^{-7} - 10^{-9} a (both systems were developed by V. P. Kornil'yev).

Recording was possible on several channels simultaneously.

The experimental animals were white rats weighing 150-200 g. Platinum electrodes were implanted under general anesthesia in the sensorimotor and auditory regions of the cortex, as well as in the formations of the striopallidal system.

The experiments were performed in special gas chambers with air enriched with a carefully measured amount of oxygen ("oxygen sample") piped in (20 sec). The animal was unrestrained, but within 2 days it usually became tame, tolerated the experimental conditions calmly and quickly fell asleep in the chamber. Due to the increase in oxygen concentration of the inhaled air brought about by the "oxygen sample," the intensification of the critical current caused by change in oxygen concentration at the cathode (ΔI_{cr}) was necessarily inversely propor-

tional to the amount of oxygen consumed. Thus, if the oxidative processes are very active, an additional portion of oxygen is quickly consumed and the temporary increase in critical current will be insignificant. If respiration is depressed, the same oxygen sample will markedly increase the ΔI_{cr} above the

original value. Consequently, ΔI_{cr} during an oxygen load permits exclusion of

the inevitable common background of the complex medium and makes it possible, when calculating only the hemodynamics, to evaluate the changes in intensity of the oxidative processes upon exposure of the organism to different influences.

Repeated (over several days) measurement of the absolute values of the critical current (I_{cr}) and changes therein caused by the oxygen sample (ΔI_{cr})

provided fairly complete information about the level of respiration in various parts of the brain of normal animals.

After obtaining clear-cut values of the original background of the animals, we subjected them for 10 days in succession to 15 min of vertical acceleration with a frequency of 70 cps and amplitude of 0.5 mm.

I_{cr} and ΔI_{cr} were measured before, during and for several hours after vibration.

To exclude errors due to noise and transfer of the animal from one chamber to another, preliminary control experiments were performed in which vibration and all the accompanying factors were continued. /131

The resultant data were processed by the methods of nonparametric statistics.

Results

From the very first few seconds of exposure to vibration the animals displayed a marked orienting reaction. However, the motor reaction generally ceased almost immediately. The animals cowered motionless on the floor of the chamber during the first 10 min. A minute or two later, motor activity developed in many animals, as they began to rush about and squeak. This reaction disappeared as soon as the vibration was halted. The orienting reflexes weakened, and the animals remained inhibited for about 15 min. Then the external differences from the control animals disappeared. Some rats had an epileptoid seizure toward the end of or immediately after vibration.

Investigation of the I_{cr} characterizing oxygen in the brain tissues of the experimental animals showed that pO_2 decreased in most of them almost as soon as vibration was started.

This decrease was specific for vibration, because this phenomenon did not occur in the control group. The differences in both groups were significant with $P < 0.05$ (according to the median criterion). The value of the current started to increase the 10th minute, but returned to the original level as soon as the vibration was halted. Investigation of oxygen tension in the brain tissues of vibrated animals showed that there were two kinds of reactions: (1) a distinct decrease in pO_2 during the first 5 min of vibration, followed by an abnormal increase; (2) a more or less perceptible increase in pO_2 during 132 vibration. The same animal might have reacted either way on any given day and, conversely, changes in pO_2 might have been in the same or different directions in different regions of the brain on the same day (fig. 1). However, in the great majority of cases pO_2 decreased in different regions under the influence of vibration. Table 1 shows the distribution of reactions of the first and second types in percentages of the total number of experiments.

It is evident from the table that in the great majority of cases the reactions to vibration were of the first type. They were most alike in the sensorimotor cortex, where I_{cr} and therefore pO_2 decreased in 80 percent of the cases as soon as vibration was started. The greatest dissimilarity of reactions occurred in the auditory cortex, where pO_2 decreased during vibration in only 65 percent of the cases (table 1A). After repeated exposures, the cortical 133 regions exhibited a tendency for reactions of the first type to increase. However, the motor subcortex showed more reactions of the second type (table 1B).

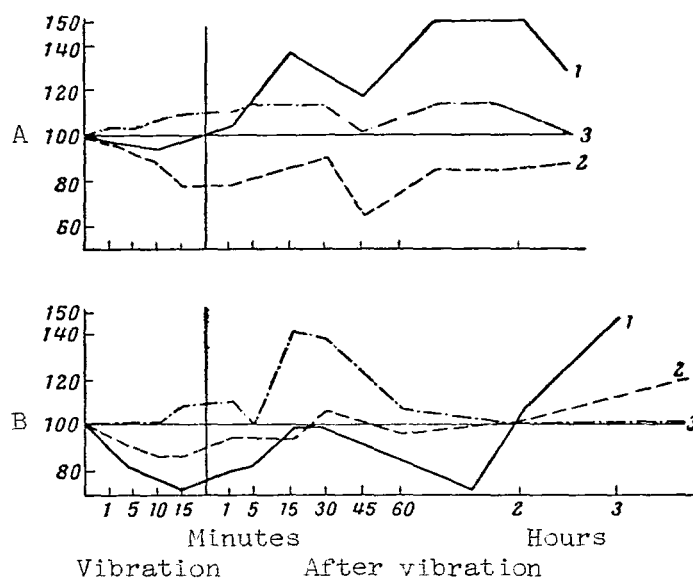


Figure 1. Change in values of I_{cr} during and after vibration

in percent of original level (rat No. 72).

A--1st day of vibration; B- 10th day; Curve 1--in auditory cortex; Curve 2--in sensorimotor cortex; Curve 3--in strio-pallidal formations. Abscissa--time in minutes and hours; ordinate--value of I_{cr} in percent of original level.

TABLE 1. NUMBER OF INSTANCES (IN PERCENT OF TOTAL NUMBER OF OBSERVATIONS) OF INCREASE OR DECREASE IN I_{cr} DURING VIBRATION.

Region investigated	A (1st-2nd-3rd day of vibration)		B (8th-9th-10th day of vibration)	
	Decrease	Increase	Decrease	Increase
Auditory cortex	65	35	74	26
Sensorimotor cortex	80	20	85	15
Motor cortex	74	26	67	33

Within 10 min of the start of vibration, pO_2 in the brain regions under study began to increase, sometimes achieving or exceeding the normal level. The maximum increase in oxygen tension occurred 15-30 min after vibration. This was followed by a third or restorative phase that sometimes lasted several hours when, after some fluctuation, there was a return to normal.

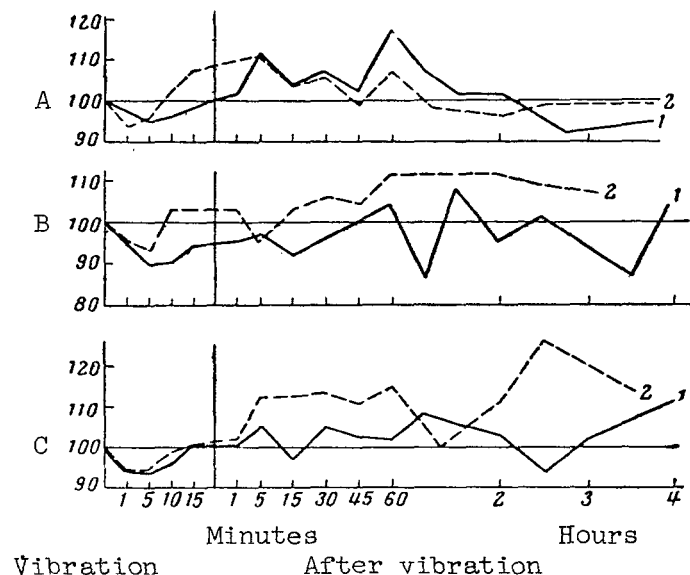


Figure 2. Change in mean values of I_{cr} during and after vibration in percent of original level.
 A--auditory cortex; B--sensorimotor cortex; C--striopallidal formations; Curve 1--mean value for first 3 vibrations; Curve 2--mean value for last 3 vibrations (8th, 9th, 10th days). Abscissa and ordinate--same as in figure 1.

TABLE 2. NUMBER OF CASES (IN PERCENT OF TOTAL NUMBER OF OBSERVATIONS) OF INCREASE OR DECREASE IN I_{cr} AFTER VIBRATION.

Region investigated	A (1st-2nd-3rd day of vibration)		B (8th-9th-10th day of vibration)	
	Decrease	Increase	Decrease	Increase
Auditory cortex	86	14	67	33
Sensorimotor cortex	64	36	77	23
Motor cortex	59	41	73	27

Table 2 and figure 2 show that the phase of increased pO_2 (table 2A), especially pronounced in the auditory region, occurred after vibration in the cortex of most of the animals. In the motor subcortex, however, the number of cases of increased pO_2 was approximately equal to the number of cases of decreased pO_2 . After repeated exposures (table 2B) there was a tendency for the

number of cases of increased pO_2 to rise in the sensorimotor cortex and motor subcortex. The reverse took place in the auditory cortex. The extent of the changes also varied with the number of exposures. It is evident from figures 2A and B that the greater the number of exposures, the earlier the phase (of shift to the left in the auditory and sensorimotor regions of the cortex) set in, and the wider it was in amplitude (figs. 2B and C). However, this pattern was not immediately apparent. We had the impression that the reaction to the second exposure was generally even weaker with respect to change in I_{cr} than the reaction to the first exposure (fig. 3), especially in the auditory cortex.

In some animals pO_2 changed spasmodically rather than gradually, /134
passing through periods of apparent normalization. It was only by comparing the effect of the first exposures with the last, as mentioned before, that we were able to detect any change in the development of the entire process. More than 10 exposures seem to be necessary before distinct and irreversible changes can be seen in the oxygen tension of brain tissues after vibration.

Analysis of the changes produced by vibration in the oxygen consumption of brain tissues revealed the presence of three successive phases, as in the case of I_{cr} : (1) increased consumption of oxygen characterized by decrease in ΔI_{cr} ; (2) decreased consumption of oxygen due to increase in ΔI_{cr} ; (3) period of restoration during which the oxygen sample returned to normal.

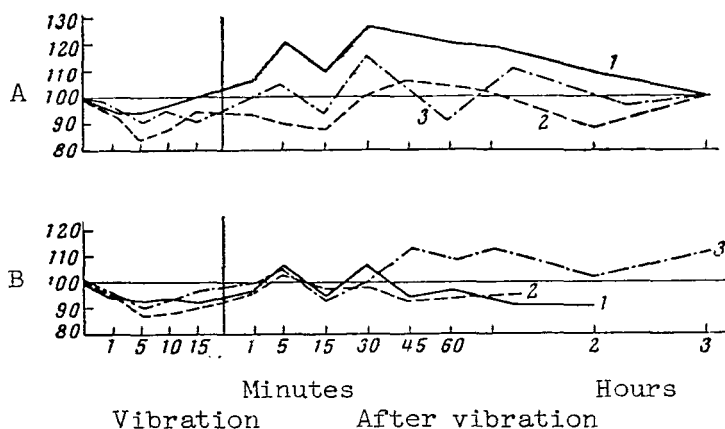


Figure 3. Change in mean values of I_{cr} during and after vibration /135
in percent of original level.
A--1st vibration; B--2nd vibration. Other symbols same as in figure 1.

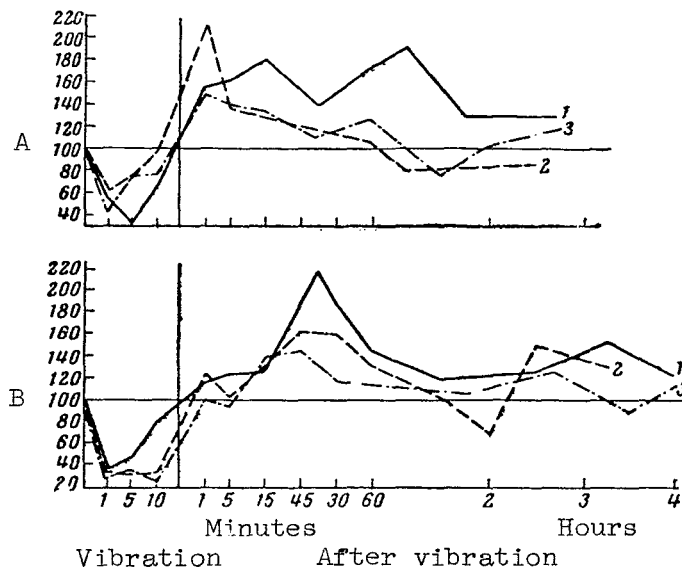


Figure 4. Change in mean values of ΔI_{cr} during and after vibration.

A--1st vibration; B--2nd vibration. Ordinate--value of ΔI_{cr} in percent of original level. Other symbols same as in figure 1.

Determination of the mean values of ΔI_{cr} during the first exposure to vibration showed that it decreased mostly in the sensorimotor cortex and motor subcortex during the first minute. The decrease was more pronounced in the subcortex (ΔI_{cr} was 38 and 55 percent below normal in the sensorimotor cortex and subcortex, respectively). In the auditory cortex, the maximum decrease in ΔI_{cr} occurred later (in the 5th min), but it was less than in the other two regions (ΔI_{cr} decreased 85 percent, fig. 4).

The return to normal started while vibration was still being applied, between the 5th and 10th min. Thus, the first phase lasted some 3-5 min. The second phase immediately followed the cessation of vibration. After the first exposure, it was most pronounced in the sensorimotor cortex (24 percent above normal), least pronounced in the motor subcortex (150 percent below normal). The maximum in these two regions occurred during the first minute following the cessation of vibration, after which there was a gradual return to normal. This process was usually spasmodic, with alternating periods of fairly sharp decrease and increase in oxygen consumption by the brain tissues (ΔI_{cr} increased and de-

creased accordingly (fig. 5). However, when the individual values were averaged (fig. 4), this irregularity was not so apparent. Sometimes a second maximum clearly developed (fig. 4B).

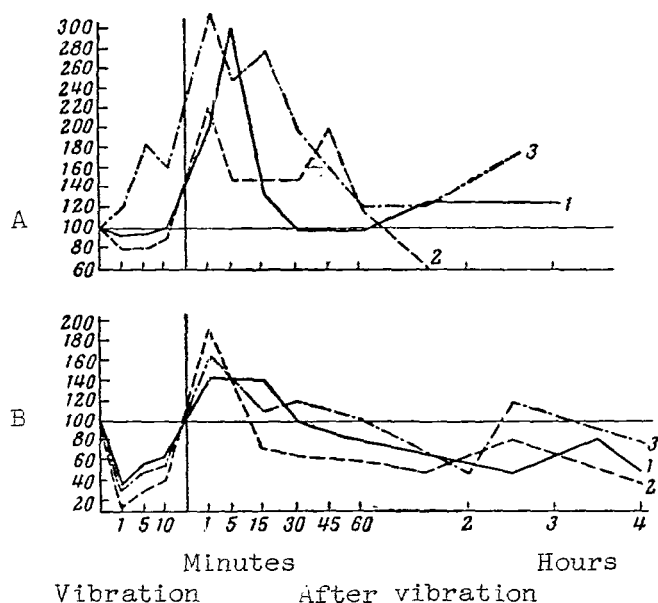


Figure 5. Change in values of ΔI_{cr} during and after vibration (rat No. 78).

A--1st vibration; B--3rd vibration. Ordinate--value of ΔI_{cr}

in percent of original level. Other symbols same as in figure 1.

The duration of the phase of increased oxygen consumption in the auditory cortex was much longer than in the other regions. After the second exposure, the first phase set in just as quickly and with equal intensity in all regions, but it lasted longer than after the first exposure. There was no return to normal in the sensorimotor cortex and motor subcortex throughout the period of exposure to vibration. The start of the second phase shifted in all the regions more to the right (than with the first exposure), i.e., the depression phase set in somewhat later than in the first case (fig. 4).

A comparison of the mean values obtained for all the animals during the first 3 and last 3 vibrations reveals that this shift in the second phase was a general tendency of the sensorimotor cortex and motor subcortex, which became manifested and intensified after repeated exposures (figs. 6B and C). The maxima of the rises did not coincide in time and, in fact, they were at different levels. They increased in the sensorimotor cortex and motor subcortex after repeated exposures, both in amplitude and in duration of the depression phase as compared with the situation after the first exposure.

The pattern was reversed in the auditory cortex. The changes in oxygen consumption were much more pronounced after the first vibrations, and they leveled out after repeated exposures (fig. 6A). These changes were statistically significant ($P < 0.05$ according to the median test).

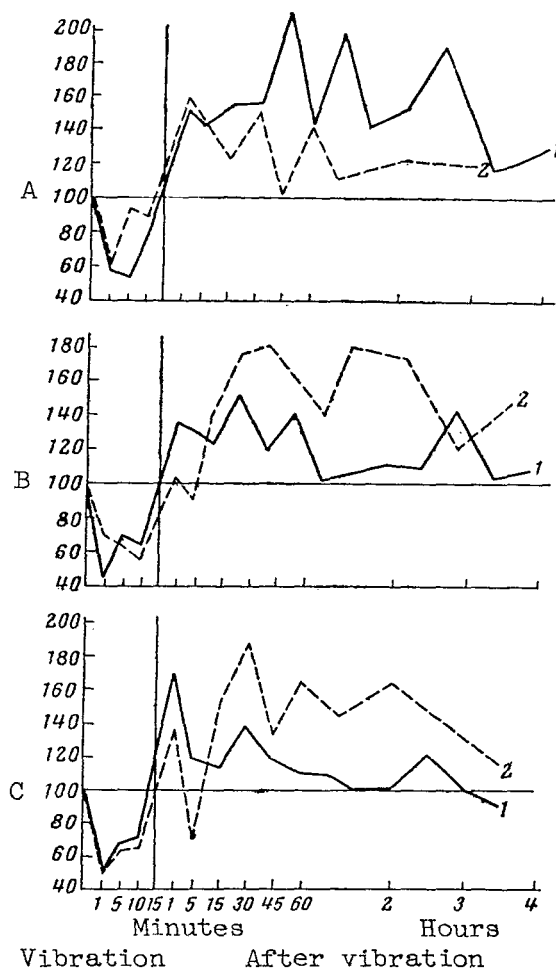


Figure 6. Change in mean values of ΔI_{cr} during and after vibration in percent of original level. Ordinate--value of ΔI_{cr} in percent of original level. Other symbols same as in figure 2.

However, despite the common direction of the process, there were marked individual differences in the development and alternation of phases, as well as in whether or not they occurred in the same animal after repeated exposures.

This was particularly true of the first phase, which set in while vibration was being applied.

In some animals, the phase of increased oxygen consumption was noted in all the regions investigated in 100 percent of the cases. In others, the phase did not appear, but the phase of decreased oxygen consumption developed immediately.

TABLE 3. NUMBER OF CASES (IN PERCENT OF TOTAL NUMBER OF OBSERVATIONS) OF INCREASE OR DECREASE IN ΔI_{cr} DURING AND AFTER VIBRATION.

Region Investigated	A (1st-2nd-3rd day of vibration)				B (8th-9th-10th day of vibration)			
	Phase I		Phase II		Phase I		Phase II	
	Decrease	Increase	Increase	Below normal	Decrease	Increase	Increase	Below normal
Auditory cortex	85	15	91	9	80	20	100	0
Sensorimotor cortex	89	11	68	32	93	7	100	0
Motor subcortex	85	15	90	10	94	6	92	8

In still other animals, this pattern was not very pronounced and it was observed in 50 percent of the cases.

Moreover, the reaction to vibration in different regions of the brain may have been either the same or different in the same animal, while oxygen consumption was high in one portion and low in another (fig. 5). This was also true of the second phase. Simultaneous control experiments showed that such phasic behavior was characteristic only of the animals subjected to vibration. /138

The development of these phases varied in different portions of the brain. /139

During the first few exposures the phase of increased oxygen consumption occurred in 85-89 percent of cases (table 3A, I) in all regions investigated. After repetition of vibration, it developed in the sensorimotor cortex and motor subcortex in 93-94 percent of cases. In the auditory cortex, however, the variance of the responses increased slightly (table 3B, I).

The development of the state characterized by a decrease in oxygen consumption after the first few vibrations (Phase II) was most pronounced in the auditory cortex and motor subcortex (90-91 percent). In the sensorimotor cortex, however, oxygen after vibration remained abnormally high in 32 percent of the cases (table 3A, II). Repeated exposures caused a reaction only of the second type (table 3B, II).

Thus, repeated vibration reduced the variations in responses during both the first and the second phases (particularly so in the latter).

Investigation of hematological indices in the animals repeatedly exposed to vibration showed no significant changes of any duration (from day to day) either in the blood formula or in liquid blood.

But immediately after vibration (30-60 min later) there was a sharp drop in the lymphocyte count (24 percent below normal) in 80 percent of cases. There was a total or partial return to normal or even a fairly pronounced lympho- /140 cytosis (in 60 percent of cases the number of lymphocytes was 40 percent above normal) 4-5 hours after vibration. No distinct changes were observed in the blood formula. In some cases, there was a slight increase in the number of segmentonuclear neutrophils and decrease in the number of lymphocytes, or vice versa. Finally, some of the animals exhibited no changes at all.

Discussion

Analysis of the results of our experiments clearly shows that the oxidative processes distinctly react to vibration. The start of vibration is generally accompanied by a decrease in oxygen tension in brain tissue and consequent increase in oxygen consumption. A similar, but much more transient phenomenon was noted by N. Ya. Kopyt (1961), who made oxyhemometric measurements in man. During the first 2 min of vibration he observed a 3 percent decrease in oxygen saturation of arterial blood, followed by a rapid return to normal or even 2-3 percent increase above normal. The author ascribes this to reflex respiratory standstill in response to vibration (phase I changes) in the presence of good compensatory reaction of the organism (phase II--change in oxygen saturation).

A comparison of Kopyt's findings with other published data and with the results of our own experiments led us to seek another explanation. Such slight and transient changes during vibration are probably due to the physical characteristics of the vibration (frequency 10 cps) which lie below the spectrum of frequencies which have the greatest effect on the organism. This explanation is quite plausible in the light of the data of other authors, who found in most cases that respiration accelerated (by 71-95 percent) rather than slowed during the first 5 min of respiration, with a 47-84 percent increase in depth (Borshchevskiy et al., 1958; Lebedeva and Tsui Chun-shan, 1958; Tsui Chun-shan, 1957). According to the data of these and other authors, blood pressure rose during the first 10 min with spastic phenomena in the small blood vessels. Study of systemic gas exchange in animals after general vibration (Lebedeva, 1957; Karchmazh, 1962) also revealed an abnormal increase in 88 percent of the cases, followed by a decrease after more prolonged stimulation.

V. A. Uglov et al. (1935) mention a marked intensification of metabolism during and after vibration. In view of the increased motor activity of /141 the animals during the first 2 weeks of exposure to vibration, these authors relate the intensification of gas exchange and metabolism following vibration to an increase in muscle tone, caused by the continuous inflow of impulses from the central nervous system. These impulses are known to alter tissue metabolism, without significantly affecting its specific function.

We also must not underestimate the reflex reaction of the cardiovascular and respiratory systems to vibration, which influences both the metabolic rate of the entire organism and the degree of oxygen saturation of blood and brain tissue.

Investigation of gas exchange after vibration (Lebedeva, 1957) showed that it remained high in some animals for some time, whereas it quickly returned to normal in others. A similar pattern was noted by N. Ya. Kopyt (1961), who found that oxygen saturation of arterial blood decreased during the first 10 min after vibration, due, in his opinion, to increased oxygen consumption by the tissues.

However, the results of this study show that once vibration is halted, the brain regions in question may exhibit a sharp lowering of the level of oxygen consumption, following a slight increase in oxygen tension. Thus, the oxidative processes that take place in the brain and other tissues at this time may proceed in different directions.

Inhibition of the energy processes in brain tissues with increased oxygen consumption elsewhere in the organism suggests that this phenomenon is not the result of change in the oxygen supply of brain tissues, but a reflection of the specific state of nervous tissue developing in response to vibration.

On this basis it is reasonable to assume the following mechanism of action of vibration on the oxidative processes in the brain.

Under the influence of vibration, numerous impulses from a variety of receptors, especially the proprioceptors, flow to the central nervous system, exciting first the centers of vibration sensitivity and then the cortex, thereby intensifying brain metabolism. This is apparently the reason that oxygen tension decreases in the brain, while oxygen consumption increases. The immediate reflex of the cardiovascular system causes the oxygen saturation of arterial blood to increase. Nevertheless, owing to this state of the higher divisions of the brain, the excess oxygen is immediately consumed by the 142 brain tissues, so that ΔI_{cr} falls sharply, sometimes to zero.

The further entry of impulses into the cortex may give rise to a focus of protective inhibition, due to overexcitation of the nerve cells. Despite the secondary increase in oxygen saturation of arterial blood and, consequently, of brain tissue, this period is marked by decreased consumption of oxygen in the brain regions under study.

The restorative period is apparently characterized by regular alternation of inhibition and normalization of excitation, which accounts for the phasic nature of the changes in the oxidative processes in the brain at this time. However, as stated before, there were some cases in which oxygen tension and oxygen consumption by nervous tissue changed in a different way under the influence of vibration. For example, in some animals the phase of high pO_2 and low oxygen consumption (increase in ΔI_{cr}) set in during vibration, whereas in others it did not occur at all, even after vibration, and it took a long time for the oxidative processes to become normal. Such a variation in responses seems to be due to the typological characteristics of the animals and the original functional state of their nervous system. The nerve cells may become overexcited very rapidly in vibrated animals without fairly strong inhibitory and excitatory

processes, so that the oxidative processes in nervous tissue are immediately affected. However, in vibrated animals with strong excitory processes, protective inhibition apparently does not occur at all.

Another factor to be considered is the animals' orienting reaction to vibration, which may intensify its effect. Prolongation of the first phase and increase in reactions of this kind, as well as the shift of the second phase to the left as early as the second or third exposure to vibration, are apparently indicative of both a gradual decrease in the orienting reaction and the development of compensatory processes. The subsequent course of the reaction to vibration confirms the fact that it is a question of compensation rather than adaptation.

We mentioned earlier that the second phase sets in sooner after repeated exposures and is more intense. This could not happen if there were adaptation. Owing to the limitations of the compensatory mechanisms, their role seems /143 to diminish after some time. Protective inhibition develops at the same time in the higher portions of the brain, due to overexcitation of the nerve cells following gradual weakening of the inhibitory process. Such protective inhibition is much more pronounced than during the first few days after vibration.

This state can probably be interpreted as a form of circular neurosis (I. P. Pavlov), when the nervous system is overstrained. Then the amount of time required for rest may be insufficient and, depending on the degree of weakening and intensity of inhibition, inhibition may persist for a long time. The considerable individual fluctuations observed in each animal on different days after repeated exposures are obviously related to the original functional state of its central nervous system.

It also follows from our data that the various regions of the brain in the same animal may react differently to vibration at the same time.

It is evident from table 1 that most deviations from the typical pattern of decrease in pO_2 during the first 3 exposures occurred in the auditory cortex.

It was here that the second phase of increase in pO_2 (table 2) was most pro-

nounced. There are numerous references in the literature to the great frequency with which hearing is impaired by vibration. It sharply lowers the threshold of hearing and slows its restoration. The auditory center may be stimulated: (a) directly from the auditory apparatus because vibration is always associated with noise; (b) by stimulation of the vestibular apparatus; (c) by induction with general excitation of the cortex. A focus of greater excitation is created here than in the other regions investigated, and consequently parabiosis easily develops. However, repeated exposure to vibration has the result that this center adapts, at least to the noise component, because a comparison of the results obtained after 8-9-10 exposures (figs. 2 and 6) shows a striking increase in this region in cases of decreased oxygen consumption during vibration and a decrease in the number of cases of inhibition developing after vibration.

Thus, all these data indicate, first, that excitation varies in intensity in different parts of the brain; second, that there is no adaptation to

vibration in the sensorimotor cortex or motor cortex; third, that compensatory processes arise as early as the second exposure to vibration.

Conclusions

1. Exposing rats one or more times to vibration (frequency 70 cps, /144 amplitude 0.4 mm, time of exposure 15 min) results in the development of 3 successive phases: (1) decrease in oxygen tension and increase in oxygen consumption by brain tissues; (2) increase in oxygen tension and decrease in oxygen consumption by the same tissues; (3) restorative period.

2. Repeated vibration with the same parameters prolongs the phase of increased oxygen consumption, while prolonging and intensifying the phase of decreased oxygen consumption by the same tissues.

3. Despite the significant, common direction of the process arising under the influence of vibration, there are substantial individual fluctuations in oxygen tension and consumption.

4. Repeated vibration reduces individual deviations in development of the process through the 3 phases.

5. The changes in level of oxygen consumption differ in the different divisions of the brain as a result of vibration.

6. Vibration produces distinct changes in the liquid blood of rats.

COMBINED EFFECT OF GENERAL VERTICAL VIBRATION AND IRRADIATION
ON THE OXIDATIVE PROCESSES IN THE BRAIN OF RATS

L. D. Luk'yanova

ABSTRACT

Changes of oxidative processes in cerebral tissues of animals (rats) exposed to vibration with subsequent irradiation proceeded differently than those of animals subjected to each effect separately. Summation effect induced by vibration was not observed. Survival of animals in the second case was significantly higher than that in the group of irradiated animals.

A parallelism between the functional state of nerve centers of irradiated animals and oxidative processes in the brain was observed. The mechanism of the combined effects of vibration and irradiation on oxygen consumption by cerebral tissue is discussed.

We know a great deal about the effect of radiation on the organism, /145 but little about the effect of radiation combined with vibration, acceleration or other factors. A. N. Ganshina (1961) showed, on the basis of pathologico-anatomical data, that vibration intensifies the effect of acute irradiation without significantly changing the effect of fractional irradiation.

Z. I. Apanasenko notes that vibration has a distinct effect on the spontaneous electric activity of muscles in the hind legs of irradiated guinea pigs and on the latent period of the myoelectric reaction after vestibular stimulation. This was also the conclusion of M. A. Kuznetsova, who studied changes in the latent period of the defense flexor reflex. These two investigations exhaust the literature dealing with the combined effect of vibration and irradiation. No attention has been paid to the intensity of the oxidative processes as a result of the combined action. Yet the problem is an extremely important one because the oxidative processes, i.e., tissue respiration, are sources of energy required for the performance of a great variety of physiological functions and the execution of the normal activity of all the cellular elements in the body.

The purpose of this study was to investigate the effect of general vertical vibration and irradiation on oxygen tension and oxygen consumption in brain tissues of the white rat. Vibration was applied under the following conditions: frequency 70 cps, amplitude 0.4 mm, duration of stimulation 15 min. The

animals were irradiated with a lethal dose of 600 r from a RUP-1 machine, dose rate 22-43 r/min, time of rotation 15-25 min, distance 45 cm, filters 0.5 mm Cu + 0.75 mm Al.

The method was described in detail in an earlier article in this collection. The changes in oxygen tension were evaluated from the change in critical current (I_{cr}), and the change in level of oxygen consumption, from

the change in value of I_{cr} caused by an "oxygen sample" supplied for 20 sec (ΔI_{cr}).

Four groups of animals were investigated: (1) rats exposed to vibration followed 15 min later by irradiation with a dose of 600 r; (2) rats irradiated with a dose of 600 r without preceding vibration; (3) rats exposed only to vibration; (4) control animals. At the same time the hematological indices, weight, general clinical condition and survival rate of the animals were observed. The resultant data were processed by the method of nonparametric statistics.

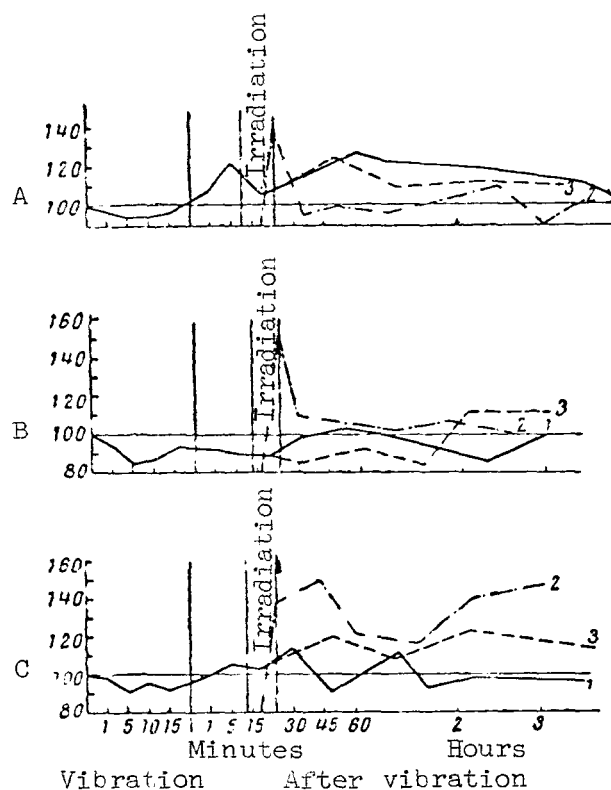


Figure 1. Change in mean values of I_{cr} during and after first vibration followed by irradiation. A--auditory cortex; B--sensorimotor cortex; C--striopallidal formations; Curve 1--animals exposed to vibration alone; Curve 2--animals exposed to irradiation alone; Curve 3--animals exposed to vibration followed by irradiation. Abscissa--time in min and hours; ordinate--value of I_{cr} in percent of original level.

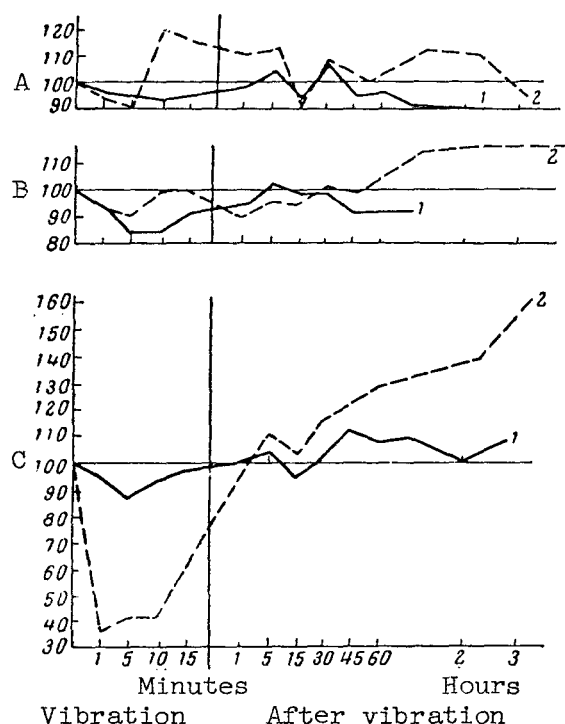


Figure 2. Change in mean values of I_{cr} during and after second vibration. Curve 1--nonirradiated animals (control); Curve 2--animals irradiated day before. Other symbols same as in figure 1.

It is evident from figure 1 that immediately after exposure all irradiated rats exhibited a perceptible increase in the critical current, an indication of increased oxygen tension in the tissues under study. The pO_2 gradually returned to normal during the next few hours, but at different rates in the various parts of the brain. /147

In the animals irradiated after exposure to vibration, the changes in oxygen tension in the tissues under study scarcely differed from the values obtained after vibration alone. There was a slight tendency for pO_2 to increase in the sensorimotor cortex and motor subcortex much later (2-3 hours after irradiation), but this difference was statistically insignificant.

After the second vibration the changes in oxygen tension in the irradiated animals differed sharply from those in the nonirradiated animals (fig. 2). For example, oxygen tension during vibration decreased in the auditory cortex and motor subcortex much more than it did in the nonirradiated animals. The increase in oxygen tension after vibration was also much greater in all regions /148

investigated, and in the regions associated with motor activity it failed to return to normal even after 3-4 hours. Oxygen tension started to increase appreciably in the auditory cortex even before vibration was halted, and the increase persisted with periodic fluctuations for about 3 hours thereafter.

The dynamics of the changes in oxygen tension in brain tissues as radiation sickness developed in the animals exposed to both vibration and radiation was also peculiar. A gradual decrease in oxygen tension in the brain was noted several days after irradiation in all experimental animals. However, in those subjected to the combined action, these changes were much more spasmodic. In the subcortex, for example, oxygen tension with marked fluctuations in either direction fluctuated around the normal level (fig. 3).

Even sharper differences were revealed by an analysis of the changes ^{/149} in ΔI_{cr} , which reflects changes in oxygen consumption by brain tissues. The

rate of oxygen consumption is known to decrease in irradiated animals immediately after exposure (Snezhko, 1960). Our investigations confirmed this ^{/150} phenomenon. It is evident from figure 4 that within 5 min of irradiation there was extreme inhibition of the rate of oxygen consumption by the tissues under study, against a background of increased oxygen tension in the same tissues. However, in the animals exposed to vibration, oxygen tension in most cases was almost normal within a few hours of the action, but in the irradiated animals the rate of oxygen consumption remained well below normal, despite the slight decrease in ΔI_{cr} within 30 min. of exposure. There was no correlation between

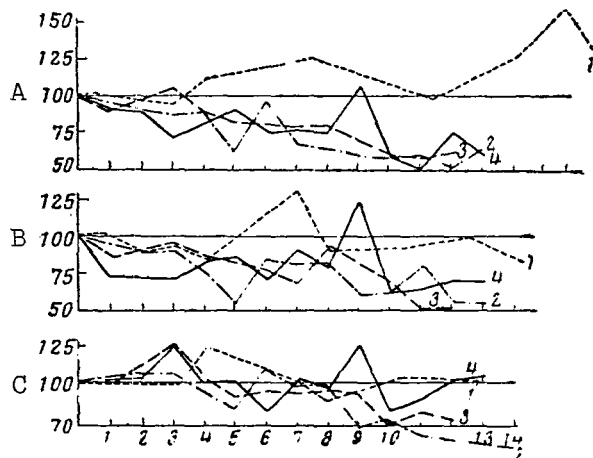


Figure 3. Dynamics of change in mean values of I_{cr}

on different days in animals exposed to vibration and irradiation and to vibration alone.

Curve 1--control animals; Curve 2--animals exposed to vibration alone; Curve 3--animals exposed to irradiation alone; Curve 4--animals exposed to vibration and then to irradiation. Abscissa- time after action in days. Other symbols same as in figure 1.

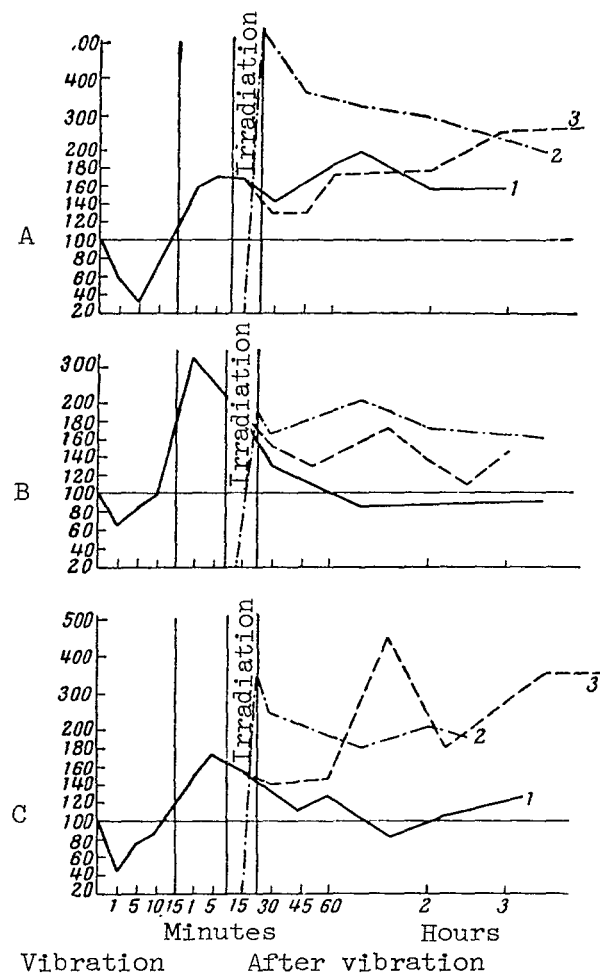


Figure 4. Change in mean values of ΔI_{cr} during and after first vibration followed by irradiation. Curve 1--animals exposed to vibration alone; Curve 2--animals exposed to irradiation alone; Curve 3--animals exposed to vibration followed by irradiation. Ordinate--value of ΔI_{cr} in percent of original level. Other symbols same as in figure 1.

the changes in the various parts of the brain. The greatest abnormalities were noted in the motor subcortex and auditory cortex.

The pattern was different in the animals subjected to vibration and then irradiated. Due to suppression of the oxidative processes in the brain following vibration, irradiation was carried out against a background of decreased

oxygen consumption by the brain tissues. However, the condition did not progress, i.e., there was no summation of the effects of radiation and vibration. The process was in the same direction as in the animals subjected to vibration alone, and it took place the first hour at the same level (fig. 4). A marked increase in ΔI_{cr} and, consequently, corresponding decrease in the rate of oxygen consumption took place only 1-2 hours later, and exclusively in the auditory cortex and motor subcortex.

The changes that resulted from the second vibration applied the day after irradiation scarcely differed from those noted in the animals subjected to vibration alone. There was merely a slight (statistically insignificant) decrease in the response in the cortical regions at the time of vibration. Oxygen consumption simultaneously decreased in the motor subcortex (fig. 5).

The dynamics of change in ΔI_{cr} during the first few days after irradiation was not identical in different parts of the brain in the irradiated animals and

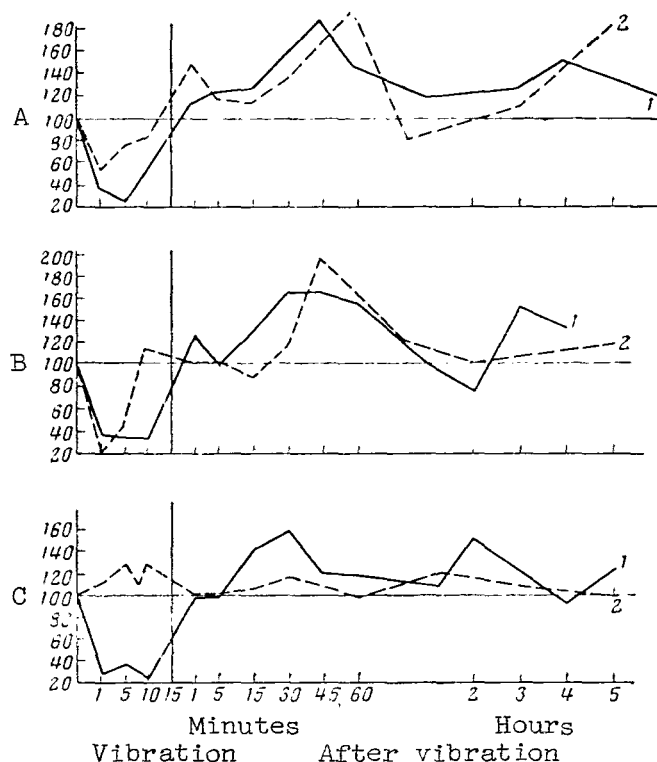


Figure 5. Change in mean values of ΔI_{cr} during and after second vibration.

Curve 1--nonirradiated animals (control);

Curve 2--animals irradiated day before. Ordinate--value of ΔI_{cr} in percent of original level. Other symbols same

as in figure 1.

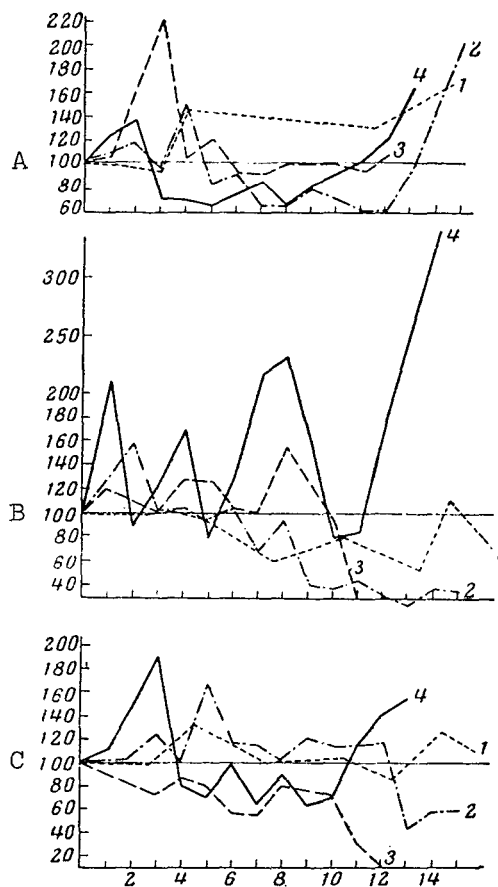


Figure 6. Dynamics of change in mean values of ΔI_{cr}

on different days in various groups of animals. Curve 1--control animals; Curve 2--animals exposed to vibration alone; Curve 3--animals exposed to irradiation alone; Curve 4--animals exposed to vibration followed by irradiation. Abscissa--time in days. Ordinate--value of ΔI_{cr} in percent of original level.

Other symbols same as in figure 1.

in those subjected to the combined action (fig. 6). Oxygen consumption in the cortical regions dropped quite perceptibly in the first group of animals during the first few days after irradiation. However, in the animals subjected to vibration, this also occurred after the very first action. But the subsequent state of increased oxygen consumption, which persisted for several days, was even more pronounced in these regions in the vibrated animals than in the irradiated animals. Just before the irradiated animals died, the rate of oxygen consumption again dropped sharply in the sensorimotor cortex. In the motor

subcortex, ΔI_{cr} started to decrease the very first day, and the process /151 intensified until the animals died, suggesting that the rate of oxygen consumption increased at this time in the region in question unlike that in the control and vibrated animals (fig. 6C).

In the animals subjected to the combined action, the changes in ΔI_{cr} could be divided into two stages. During the first 2-4 days after irradiation, the level of oxygen consumption changed in the same direction as in the vibrated animals, but their amplitude was greater. However, the changes in ΔI_{cr} then followed the changes observed in the irradiated animals, with which they coincided in phase, although of greater amplitude. It was only on the 12th day that there was a reaction directly opposite to that which occurred in the irradiated animals, i.e., a sharp decrease in the rate of oxygen consumption by the /152 brain tissues (fig. 6).

Clinical examination of the rats showed that among the animals exposed to irradiation alone, the mortality rate was much higher than among the animals exposed to irradiation after vibration. Among the former, 90 percent of the /153 animals died on the average 10 days (between the 8th and 13th days) after exposure to ionizing radiation. The hematological indices changed the day after irradiation--drop in leukocyte count, sharp increase in number of segmentonuclear neutrophils and an equally sharp decrease in number of lymphocytes (fig. 7 and table, A). As radiation sickness progressed, the leukopenia intensified. In

some cases there were about 200 leukocytes per cm^3 of blood just before the animals died. Blood was generally not taken at this time. On the third day the neutrophils and lymphocytes disappeared almost completely from the blood, with only the walls of the destroyed cells remaining. On dissection all animals were found to have pernicious anemia.

The course of radiation sickness proceeded differently in the animals exposed to irradiation after vibration. To begin with, the mortality rate was only 30 percent. Moreover, the animals died somewhat later than did those in the first group (on the 14th or 15th day). During the first 3 days all rats developed the same acute leukopenia as the irradiated animals. Starting the 3rd to 5th days, the process halted, but on the 10th day restoration of the /154 elements of the liquid white blood (fig. 7) began. However, in many rats of this group, blood coagulability was much higher than in the irradiated animals and unlike them, the number of lymphocytes started to increase by the 3rd day, reaching a maximum on the 5th day; but the number of segmentonuclear neutrophils decreased (table, B). However, by the 10th day the blood formula was largely restored.

At the height of radiation sickness, the animals exposed to irradiation after vibration sometimes showed the presence of a substantial number of immature neutrophils (about 10-14 percent) but a marked eosinophilia (about 8-14 percent) in the recovery period. Between the 15th and 25th days, the blood was completely normal in the surviving animals. In the dead animals, the changes in

the blood formula were in the same direction as in the survivors, but not as in the irradiated animals.

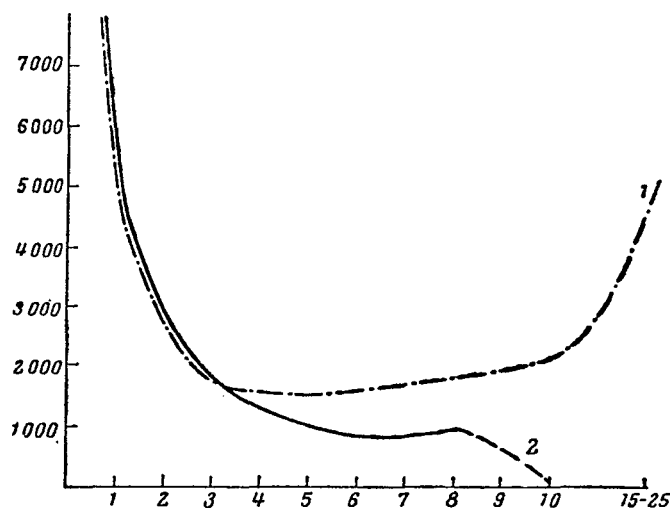


Figure 7. Dynamics of change in leukocyte count on different days in animals exposed to vibration followed by irradiation (1) and in animals exposed to irradiation alone (2).
Abscissa--time in days; ordinate--number of leukocytes in 1 cm³ of blood.

CHANGE IN NUMBER OF FORMED BLOOD ELEMENTS (IN PERCENT OF ORIGINAL LEVEL).

Day	Irradiation (A)		Vibration followed by irradiation (B)	
	Segmentonuclear neutrophils	Lymphocytes	Segmentonuclear neutrophils	Lymphocytes
1	244	8	-	-
3	Destroyed cells		65 (in 50% of cases blood contained clots)	116
5	Destroyed cells		67 (in 37% of cases blood contained clots)	129
10	Either cells were destroyed, or there was so little blood smears could not be taken		42	106
15-25	-		93	93

Discussion

Our findings suggest that there are significant differences with respect to oxygen consumption by brain tissues between animals exposed to vibration followed by irradiation and animals exposed to irradiation alone. There are fairly numerous and contradictory published data on the changes in gas exchange and metabolism in radiation sickness.

Some authors found a distinct decrease in gas exchange some time /155 after the animals were irradiated with lethal and sublethal doses of X-rays or γ -rays. Others, failing to observe this phenomenon, contended that fluctuations in gas exchange are not exclusively characteristic of radiation sickness.

There is also a reference to the possibility of some increase in intensity of gas exchange during the initial stages of radiation sickness.

Kirschner et al. (1949) were unable to detect any changes in oxygen consumption by rats immediately after they were irradiated with 54-972 r doses. But 1-3 days later they observed marked intensification of gas exchange, which was most pronounced after the use of lethal doses of X-rays (about 158 percent above normal). This was invariably followed by a decrease in gas exchange, after which the animals soon died with symptoms of acute radiation sickness.

Schneider and Braun (1963) noted the onset of a phase of increased oxygen consumption by rats (22 hours after irradiation with a dose of 600 r) only after an initial (within 3-6 hours) sharp decrease in oxygen consumption by the animals.

Somewhat different data were obtained by Ye. F. Romantsev and I. I. Ivanov (1953),¹ who demonstrated a tendency for respiratory gas exchange to decrease after 72-96 hours in mice irradiated with a dose of 600 r. During the terminal stage of radiation sickness (8th day), gas exchange decreased more than 50 percent, an invariable sign of approaching death.

Other investigators came to similar conclusions (Reprev, 1926; Bondarenko, 1961; Lyalin, 1961).

N. Blokhin (1938) showed that X-irradiation (300-750 r) of the hypophyseal region almost immediately alters gas exchange in various organs, either by increasing or decreasing it. For example, after irradiation the intensity of respiration rose in the liver, spleen, muscles and brain, while oxygen consumption by the intestinal wall and kidneys decreased.

Measurement of the rate of oxygen consumption by the "oxygen cathode" method in rabbits exposed to whole-body irradiation with a dose of 1000-1200 r (Snezhko, 1960) showed that it decreased sharply during the first 2-3 hours. In fact, in some cases the process began to develop within 5 or 10 min. After

¹Cited from I. I. Ivanov et al., 1956.

24-48 hours the level of oxygen consumption still remained below normal. It then fell, and on the following days the changes were wavelike.

In our investigations, as mentioned before, we also observed a sharp /156 decrease in oxygen consumption in rats, within minutes after they were irradiated with a dose of 600 r.

It is an established fact that oxygen tension and oxygen consumption by tissues in a living organism may reflect both the blood supply conditions of these tissues and the level of their metabolic processes. Most of the investigators of gas exchange mentioned in this study, as well as those who investigated metabolism in radiation sickness, do not rule out the possibility of a secondary decrease in activity of the respiratory processes, but they believe that the enzymatic systems of tissue respiration are not seriously injured at the time of irradiation (Ivanov et al., 1956; Cherkasova et al., 1962).

However, some attempts have been made to link the primary radiation lesions to the injury inflicted on the respiratory system of tissues by ionizing radiation. For example, Noyes and Smith (1959) showed that there is a sharp decrease in the number of mitochondria in the liver of rats 1-1/2 hours after irradiation with a dose of 1000 r. Having in mind the views of those who state that the volume of oxygen consumed is a function of the number of mitochondria. A. D. Snezhko conjectured that the increase in oxygen tension in the brain, that occurs within the first few hours of direct irradiation of brain tissue, results from depression of tissue respiration due to a decrease in the number of mitochondria. This is a possibility that cannot, of course, be denied. It is worth mentioning here that I. Belokonskiy and G. Rusev (1959) showed that changes in dehydrogenase activity and oxygen consumption in tissues set in during irradiation, and that they have a phasic quality, depending on the size of the dose.

Histological investigations also show that even 50-100 r doses may within 2 hours induce changes in nerve cells characteristic of hypoxia. These changes occur earlier than do those in the vascular system, and they vary in different formations of the brain and cortex (Aleksandrovskaya, 1958).

However, all these investigators, with the exception of Belokonskiy and Rusev, refer to changes that take place in the living organism within the first few hours of irradiation. It is quite likely, therefore, that the primary changes in oxygen consumption and tension observed in brain tissue the first minutes after irradiation may have another origin, specifically, in hemodynamic changes.

It is now generally known that local and whole-body irradiation /157 lowers peripheral arterial pressure, very sharply and quickly if lethal doses are used (Montgomery and Warren, 1951; Snezhko, 1960). But immediately after irradiation blood pressure may rise temporarily (15-30 min) and then fall sharply and persistently to 50 percent of the control values (Frank, 1955; Nefedov, 1960; Luk'yanova, 1963). The change in arterial pressure in the periphery reduces the filling of the vessels of the skin with blood and cannot help but affect the viscera. For example, V. K. Modestov (1941) notes that in the meantime blood flows to them. The hyperemia that takes place in the

viscera, against a background of low blood pressure, may induce congestion, resulting in asphyxia and complete impairment of the metabolic processes. The mass of circulating blood decreases, and this inevitably affects the blood supply of the brain. R. M. Lyubimova (1958) found that the rate of the cerebral blood flow diminishes during the few hours after irradiation.

It follows that the increase in oxygen tension and decrease in rate of oxygen consumption by brain tissues, which we observed immediately after irradiation, may be due to a brief increase in blood supply taking place at the same time. This, in turn, shows utilization of the additional amounts of oxygen arriving with the "oxygen sample" and, consequently, increases ΔI_{cr} (figs. 1 and 4). Later, despite the lowering of blood pressure that is now apparent and the decrease in oxygen tension in both plasma and whole blood (Snezhko and Vysochina, 1958), oxygen tension in the brain tissues and the value of ΔI_{cr} , although less than during the first few minutes, nevertheless are still abnormally high.

This phenomenon cannot be ascribed solely to the altered blood supply conditions. We are led to assume that the metabolic processes in the cerebral cortex change at this stage. Thus, despite the developing hemodynamic disturbances that result in deterioration of the blood supply, the brain tissues have free oxygen during the first hours after irradiation, even though its consumption is actually impaired. This is quite apparent even on the day after irradiation and it persists for several days, after which the amount of free oxygen in the brain tissues begins to decrease (fig. 3C), while the rate of consumption steadily rises (figs. 6A and C). According to L. S. Cherkasova et al., the interlinking of reactions in the chain of biological oxidation is broken some time after irradiation, resulting in impairment of tissue respiration and change in oxygen consumption. /158

A. Vatssek (1962) mentioned the reflex nature of the change in oxygen consumption of rats after exposure to irradiation.

It is now well understood that radiation lesions drastically alter the functional state and excitability of the nerve centers (Livanov, 1962). Within a few minutes of irradiation, the cerebral cortex and centers of the mesencephalon and medulla oblongata become excited as a result of an extremely sharp increase in reactivity of the receptors and ensuing intensification of the flow of afferent signals from the periphery (1st period). Subsequent activation of the cortex brings about a state of protective inhibition characterized by a sharp decrease in the biopotentials, loss of conditioned reflexes and phasic states (2nd period). Meanwhile, the excitability of the subcortical centers continues to grow and progressively intensify, even when a period of relative normalization develops in the cortex and it becomes disinhibited (3rd period). Excitation in the subcortex reaches a peak in the terminal stage and is reflected in epileptiform discharges. This state gives way to a deep disorganization of subcortical activity and paralysis, followed by a state of parabiosis, which also involves the cortex and ultimately disrupts its correlation and compensatory mechanisms (4th period).

Analysis of the dynamics of oxygen consumption by brain tissue in irradiated animals, as studied in this investigation, reveals that there is a definite parallelism between the functional state of the nerve centers and the oxidative processes in the brain. For one thing, their level varies in different parts of the brain. For example, oxygen consumption is very low in the cortex for several days after irradiation (figs. 6A and B)--this appears to coincide with the 2nd period of Livanov. Later, there is relative but quite unstable normalization of the rate of oxygen consumption (3rd period). Oxygen consumption progressively increases at this time in the motor cortex without any hint of normalization.

Thus, we see at these stages a distinct analogy and an obvious relationship between the change in functional condition of the nerve centers and the intensity of tissue respiration. And it is only in the terminal stage that there is a sharp decrease in ΔI_{cr} in the sensorimotor cortex and subcortex with consequent increase increase in oxygen consumption therein.

We failed to observe any increase in oxygen consumption in the cortical regions immediately after irradiation that might correspond to Livanov's 1st 159 period.

A comparison of the data on irradiation with the results of the combined action of vibration and irradiation reveals that the combined action has a very specific effect on gas exchange in the brain. Instead of the expected summation (increase in oxygen tension and decrease in rate of oxygen consumption after vibration + increase in oxygen tension and decrease in rate of consumption after irradiation), both values continued to change during the first 30-60 min after irradiation in almost the same way as after vibration alone (figs. 1 and 4). However, some time afterward the level of oxygen consumption began to rise and a few hours later even exceeded the values obtained for the irradiated animals.

The changes in oxygen tension were less clear-cut, but they also showed no sign of summation. This implies that the phenomenon of protective inhibition, that arose after vibration and created a phase of inhibition in the brain respiratory processes, prevented the development of all factors responsible for changing these processes in the irradiated animals, despite the increase of free oxygen in the brain tissues at this time and the possible manifestation of the oxygen effect as a result.

The picture that developed under the influence of vibration on the day after irradiation indicates that there was some weakening of the functional activity of the nerve centers, because the inhibition phase set in sooner in all brain regions under study than it did in the nonirradiated animals.

This plus the fact that oxygen consumption was much lower the first few days after irradiation in the animals subjected to the combined action than in the other animals indicates that the functional activity of the nerve centers was considerably weaker. Even the motor subcortex was inhibited at this time, which was not the case with the irradiated animals. Apparently, the combination of

two such powerful stimuli as vibration and irradiation immediately weakened all higher divisions of the brain to such an extent that protective inhibition developed. This was very likely the decisive factor in the subsequent development of the process. It may have blocked or at least slowed the appearance of the primary reactions which have a major influence on the outcome of radiation sickness. For 12-15 days after the combined action, the state of the nerve centers in these animals, as pointed out before, was highly unstable, with periodic normalization and repeated development of pathological states, which were sometimes even more pronounced than in the irradiated animals. However, at this time, when the latter entered the terminal state, characterized by a sharp increase in excitability of all centers and resultant sharp rise in oxygen consumption, the animals subjected to the combined action developed heightened excitability of the cortex and subcortex, accompanied by an equally sharp decrease in oxygen consumption by the tissues. /160

Thus, on the basis of the data presented in this report, we can unhesitatingly say that the original state of the nervous system is a decisive factor in the subsequent development of radiation injury.

Conclusions

1. Irradiation of animals with a lethal dose (600 r) alters the conditions of metabolism in the higher divisions of the brain, resulting in suppression of oxygen consumption by the sensorimotor and auditory regions of the cortex and motor subcortex during the first few hours after exposure.

2. Analysis of the dynamics of oxygen consumption by brain tissue in irradiated animals as radiation sickness develops revealed a marked parallelism between the functional state of the nerve centers and the oxidative processes in the brain.

3. The changes in oxidative processes in the animals subjected to the combined action of vibration followed by irradiation develop differently from the way they do under the influence of irradiation alone.

4. The survival rate among animals subjected to the combined action of vibration and irradiation is much higher than in the animals exposed to irradiation alone.

THE EFFECT OF GENERAL VERTICAL VIBRATION AND X-RAYS ON THE
NUCLEI OF BONE MARROW CELLS IN MAMMALS

Yu. S. Demin

ABSTRACT

The paper presents the results of the investigations of the effect of vibration (60-70 cps), of the irradiation with doses of 50-100 r of X-rays and of the combined effect of vibration and irradiation on the cells of marrow of mice. Vibration of animals causes an increase of disturbed mitosis due to a higher rate of chromosome cohesion. Vibration preceding irradiation does not increase the rate. Some decrease of rate of chromosome aberrations and increase of rate of chromosome cohesion was found when the combined effect of both factors was studied. The rate of disturbed mitosis in the marrow cells of mice analyzed was higher than that in control for as long as ten days.

One of the important tasks of space biology is to study the effect of spaceflight factors on the living organism. These factors include ionizing radiation, weightlessness, acceleration and vibration. They can affect the organism in various combinations and sequences. The possible cytological effect of these factors is especially noteworthy. /161

Numerous data are now available on the physiological and mutagenic effect of ionizing radiation (Yegorov, Bochkarev, 1955; Alexander, 1959; Dubinin, 1962). It has been shown that various kinds of radiation (α -, β -, γ - and X-rays, neutrons and protons) damage the plasmatic and nuclear structures of the cell. Mitotic activity changes (Knowlton, Widner, 1950; Yegorov, Bochkarev, 1955; Karpfel, 1961), and various mitotic disturbances appear: formation of dicentric and acentric fragments, cohesion of chromosomes, etc. (Devik, 1954; Devik and Loothe, 1955; La Cour and Rutishauser, 1954; I. M. Shapiro, Faleyeva, 1962; Dubinin and Dubinina, 1963).

As a rule, damage to the nucleus leads to disruption of the gene balance in the cell. The effect of dynamic flight factors on the cell has been studied to a lesser degree. However, the possibility is not excluded that these factors can influence the cell nucleus, or substantially alter the effect of radiation during combined action.

Many authors (Sisakyan et al., 1962; Gyurdzhian, 1962) emphasize that the combined effect of space flight factors (radiation and dynamic factors) on

heredity may differ from the effect of radiation alone. There are experimental data favoring this assumption. Sax (1943) centrifuged *Tradescantia* microspores during and after irradiation. In the first case the irradiation effect was intensified; in the second, the effect remained unaltered. Wolff and Borstell (1954) observed that centrifugation of *Tradescantia* microspores and *Vicia* radicles before irradiation reduced the effect of irradiation by approximately one half, whereas centrifugation during and after irradiation increased the effect of irradiation and the number of chromosomal aberrations. Conger (1948) exposed *Tradescantia* microspores to sound vibration with a frequency of 9,100 cps in water. Exposure to sound began simultaneously with X-irradiation and continued 5 min after irradiation had ceased. The combined action of acoustic vibration and X-rays increased the number of aberrations by approximately 25 percent. Exposure to sound alone produced no effect. Conger believes that such agents as centrifugation and exposure to sound influence the mobility of the chromosomes. They accelerate the separation of the broken ends, thus diminishing the chances of their reunion.

Basic results on the effects of space flight factors were first obtained in the Soviet Union by the experiments of the spacecraft satellite, and subsequently determined the design of a series of model genetic experiments.

B. N. Sidorov and N. N. Sokolov (1961) analyzed the frequency of chromosome rearrangements in the onion (*Allium fistulosum*) and in fennel (*Nigella damascena*) sprouts, the seeds of which had been on the spacecraft satellite. No difference was found between the experimental plants and the controls. A comparison of the germination rate, however, showed the stimulating effect of space flight. Since it is difficult to explain this stimulation by the action of cosmic radiation, the authors assume that it may have been induced by dynamic factors, particularly by vibration.

Ya. L. Glembotskiy et al. (1961) examined actinomycetes and seeds of higher plants after space flight. The viability of the radiation-resistant strain of actinomycetes had increased 6 times after the flight; in the radiation-sensitive stock it had decreased to 1/12th. The percent of chromosome arrangements was greater in the sprouts of all the varieties of seeds examined than in the controls. A significant difference from the controls, however, was observed only in the *Spartacus* pea and in corn.

E. A. Abeleva, G. P. Parfenov and Yu. A. Lapkin (1962) found a significant increase in the frequency of crossovers in *Drosophila* males after the space flight. They established in ground-level experiments that the crossing-over in the sex cells of *Drosophila* males can be induced by low-quality vibrations.

N. P. Dubinin et al. (1962) noted the phenomenon of primary nonbreakage of X chromosomes in *Drosophila* females after space flight. The effect was long-lasting and differed from the comparatively brief aftereffects which followed X-ray irradiation. According to the authors, the reason for the increase in the number of nonbreakage, which affects the mechanism of cell division, is caused by weightlessness during flight, the vibration of the spacecraft, or a more 163 complex combination of factors.

G. P. Parfenov (1961) found an increase in dominant lethals in the spermatids of *Drosophila* males returned from space flight. One of the possible factors increasing lethals could be vibration.

Ya. L. Glembotskiy, E. A. Abeleva et al. (1962) have shown that space flight increases the frequency of sex-linked recessive lethals in *Drosophila* with statistical significance. Cytological examinations demonstrated the point character of induced mutations. Point mutations and the frequency of mutating action in the spermatids, as compared to the mutation frequency in the spermatozoa, suggest cosmic radiation as a possible cause.

A detailed cytological analysis was made in mammals for the first time by M. A. Arsen'yeva, V. V. Antipov et al. (1961). These authors studied the chromosomal disturbances in the bone marrow of mice. They noted an increased frequency of disturbed mitoses, which significantly exceeded that of the control cases, even on the 60th day after flight. The pattern of disturbed mitoses differed from the one obtained after X-ray irradiation: most of the damage appeared in the form of bridges without loose fragments, which suggested a state of chromosome coherence instead of rupture. Since the total dose of radiation registered during the flight of the spacecraft satellite was insignificant, the authors presumed that the bone marrow disturbances could have been caused by other factors, for example, by vibration and acceleration.

Thus, a number of authors attribute the abnormalities observed in the cytogenic experiments of the spacecraft satellite to vibration. Model experiments were performed on the ground to determine the actual role of vibration in the phenomenon observed.

E. A. Abeleva, G. P. Parfenov and Yu. A. Lapkin (1962) induced a crossing-over in *Drosophila* males by means of low-frequency vibrations. G. P. Parfenov (1961), in experiments of vibration effects, obtained an increase of dominant lethals in *Drosophila* males.

In analyzing the *Drosophila* material returned from space flight and the model vibration experiments, Ya. L. Glembotskiy and G. P. Parfenov (1962) arrived at the conclusion that the mutations produced by chromosome rearrangement, i.e., the dominant lethals, may be largely due to the vibration of the rocket. It is possible that this factor contributed also to a certain extent to the induction of recessive lethals; for a number of reasons, however, induction by cosmic radiation is more probable.

In the experiment of M. A. Arsen'yeva, V. V. Antipov et al. (1961) the vibration of mice at a frequency of 70 cps resulted in the increase of disturbed mitoses in the bone marrow. The pattern of the disturbances was specific: approximately two-thirds of the disturbed mitoses showed chromosome coherence, only one-third rearrangement. At the end of the first day after vibration, the animals (excluding controls) presented 21 percent disturbed mitoses. An increased frequency of disturbances was observed until the 30th day after the start of the experiment.

Although our data on the possible influence of low-frequency vibration on heredity are preliminary, it seems to us that they provide sufficient reasons

for a more detailed study of this problem. The object of this study was a detailed cytological examination of the bone marrow cells of mice at various moments following the vibratory action, and the analysis of the combined actions of vibration and radiation.

Material and Method

White stockbred male mice weighing 18-20 g were used. The animals were exposed to X-irradiation with doses of 50 and 100 r.

Vibratory action was administered at frequencies of 60 and 70 cps on the vibrator A-20 of the Acoustic Institute system, USSR Academy of Sciences. Each mouse was placed in a separate cell of the metal cassette. The vibration was vertical.



Figure 1. Microphotograph of mitoses in mouse bone marrow cells, magnification X1350. a--normal anaphase; b--anaphase with fragments; c--chromatid bridge and fragments; d--chromosomal bridge; e and f--chromosome coherence.

The mice were irradiated before and after vibration, the interval between irradiation and vibration being 3-5 min.

The animals were sacrificed by decapitation. Fixation of the thigh and shin bones was done in acetalcohol at about 0°C temperature.

The staining for microscopic examination was done by the Feulgen method or by acetocarmine.

In the total preparations (fig. 1) disturbed mitoses were counted in the anaphase and early telophase. Moreover, the mitotic activity (mitotic index) of the bone marrow cells was determined in a series of animals. The control animals were sacrificed at the same time.

Results and Discussion

Effect of vibration (at 60 cps) and irradiation with a dose of 100 r /165

The object of these experiments was to analyze the frequency of disturbed mitoses in the bone marrow of mice after combined action of vibration and irradiation, and after each of these factors separately. Examination of the mitoses was made after brief or long time periods following irradiation, the animals being sacrificed after 30 min, 5 hours, 1, 2, 3, 5 or 10 days. The vibration lasted 20 min, at a frequency of 60 cps and 0.25 mm amplitude. Irradiation was administered with doses of 100 r.

The experimental animals were divided into four groups:

- Group 1, vibration only (V);
- 2, irradiation only, 100 r;
- 3, combined action, vibration before irradiation (V + 100 r);
- 4, combined action, vibration after irradiation (100 r + V).

The biological control animals were sacrificed simultaneously with the experimental animals. The same controls were used for the first, second and third groups; their indices are given in table 1. For the fourth group there were separate controls, represented in table 2.

Comparison of the results of the groups using different controls was done under strict consideration of the control values (table 3).

Altogether 118 mice were used in the experiments, and over 66,000 cells were analyzed.

Table 1 gives the cytological analysis data of the bone marrow in the first group (V). These data show that vibration induced an increase in the total frequency index of disturbed mitoses, in all periods of examination, as compared to the controls. The difference is statistically significant in every case (table 3), except in the 5-hour and 2-day periods. It is characteristic that the frequency increase of disturbed mitoses occurred at the expense of the frequency of chromosome coherence. The percent of cells presenting chromosome rearrangements exceeded the control rate only in the 30 min period ($t = 2.4$; $0.01 < D < 0.02$); in other periods no substantial divergence from the controls were noted.

In the animals of the second group (irradiation with 100 r), the number of cells showing disturbed mitosis was sharply increased (table 1). In the early periods after irradiation (30 min, 5 h, 1, 2 days) the majority of cells presented chromosome rearrangements.

Later, the frequency index of chromosome rearrangements decreased; nevertheless, it exceeded that of the controls even on the 10th day ($t = 2.04$; $0.02 < D < 0.05$).

The maximum amount of rearrangements was observed in the animals sacrificed 5 hours after exposure. The greatest decrease in the number of cells/168 presenting chromosome rearrangements was observed during the first two days (from 63.80 to 10.26 percent). The frequency index of cells showing coherent chromosomes varied little in the later periods: at the start of the experiment it was 9.82 percent, on the 10th day 11.90 percent.

The fluctuations in intermediate periods were slight (with the exception of the "2nd day" period: here the frequency index of chromosome cohesions dropped below the control index--to 4.37 percent).

The total percent of cells with mitotic disturbances in the second group significantly exceeded that of the controls in all periods analyzed.

The third group of mice (V + 100 r) (table 1) and the fourth (100 r + V) (table 2) were exposed to the combined action of vibration and irradiation. The results obtained in these groups after analysis of the bone marrow are compared with the analogous indices of the first (V) and the second (100 r) groups.

Since no significant changes were observed in the class of chromosome rearrangements after vibration (group 1), groups 3 and 4 were compared in this index with those of group 2 only.

The variation of the frequency index of chromosome rearrangements in the third (V + 100 r) and fourth (100 r + V) groups is similar to that in the second (100 r) group (fig. 2): the maximum of rearrangements is observed at the 5th hour period; the sharpest decrease in the frequency index of chromosome rearrangements occurred during the first two days (from 54.37 to 4.14 percent in the third group, and from 57.13 to 5.25 percent in the fourth group). In the last periods the percentage of disarranged chromosome cells decreased even more, although it remained somewhat higher than in the controls.

TABLE 1. FREQUENCY OF DISTURBED MITOSES IN CELL NUCLEI OF BONE MARROW OF MICE IN FIRST, SECOND AND THIRD GROUPS.

Time of sacrifice (time after exposure)	Rearrangements, %					Chromosome coherence, %	Total % of mitotic disturbances
	Type of action	Total of rearrangements	Fragments	Bridges			
				Without fragments	With fragments		
30 min	B	3.73 ± 0.52	1.29 ± 0.30	2.44 ± 0.42	—	8.75 ± 0.83	12.48 ± 0.99
	100 p	37.41 ± 1.24	21.61 ± 1.05	11.92 ± 0.80	4.61 ± 0.54	9.82 ± 0.76	47.23 ± 1.28
	B + 100 p	18.31 ± 1.03	11.51 ± 0.85	5.01 ± 0.59	1.79 ± 0.51	15.24 ± 0.96	33.55 ± 1.26
5 h	B	2.30 ± 0.47	0.51 ± 0.22	1.79 ± 0.40	—	7.16 ± 0.75	9.46 ± 0.85
	100 p	63.80 ± 1.13	23.57 ± 0.99	19.59 ± 0.93	20.64 ± 0.94	8.44 ± 0.65	72.24 ± 1.05
	B + 100 p	54.37 ± 1.12	24.36 ± 0.97	16.13 ± 0.83	13.61 ± 0.77	13.61 ± 0.77	67.98 ± 1.04
1 day	B	2.47 ± 0.35	0.72 ± 0.20	1.75 ± 0.30	—	13.43 ± 0.77	15.90 ± 0.83
	100 p	15.19 ± 0.85	6.58 ± 0.59	6.98 ± 0.56	1.63 ± 0.28	8.56 ± 0.66	23.75 ± 1.01
	B + 100 p	15.86 ± 0.98	6.69 ± 0.67	7.79 ± 0.72	1.38 ± 0.30	12.01 ± 0.87	27.87 ± 1.21
2 "	B	2.50 ± 0.61	0.47 ± 0.26	2.03 ± 0.56	—	8.44 ± 1.10	10.94 ± 1.23
	100 p	10.26 ± 0.97	5.08 ± 0.49	3.66 ± 0.60	1.52 ± 0.38	4.37 ± 0.65	14.63 ± 1.13
	B + 100 p	4.14 ± 0.62	1.68 ± 0.40	2.46 ± 0.49	—	10.34 ± 0.95	14.48 ± 1.14
3 "	B	2.98 ± 0.58	0.83 ± 0.32	2.15 ± 0.50	—	10.61 ± 1.06	13.59 ± 1.18
	100 p	6.98 ± 0.77	2.54 ± 0.47	4.44 ± 0.62	—	9.69 ± 0.89	16.67 ± 1.12
	B + 100 p	3.73 ± 0.57	1.21 ± 0.33	2.52 ± 0.48	—	7.48 ± 0.79	11.21 ± 0.96
5 "	B	2.74 ± 0.49	0.78 ± 0.25	1.96 ± 0.39	—	10.92 ± 0.87	13.66 ± 0.96
	100 p	4.49 ± 0.79	1.40 ± 0.43	3.09 ± 0.65	—	11.24 ± 1.18	15.73 ± 1.36
	B + 100 p	3.16 ± 0.42	0.72 ± 0.20	2.44 ± 0.36	—	9.13 ± 0.70	12.29 ± 0.80
10 "	B	2.33 ± 0.50	0.22 ± 0.17	2.00 ± 0.46	—	10.89 ± 1.03	13.22 ± 1.13
	100 p	3.72 ± 0.63	0.23 ± 0.14	3.49 ± 0.62	—	11.90 ± 1.14	15.62 ± 1.22
	B + 100 p	2.92 ± 0.62	0.58 ± 0.26	2.34 ± 0.51	—	11.90 ± 1.10	14.82 ± 1.21
Control		2.33 ± 0.28	0.57 ± 0.17	1.62 ± 0.23	0.14 ± 0.07	6.87 ± 0.47	9.20 ± 0.52

TABLE 2. FREQUENCY OF DISTURBED MITOSES IN NUCLEI OF BONE MARROW OF MICE
IN FOURTH GROUP (100 + V).

Time of sacrifice (time after exposure)	Rearrangements, %			Total	Chromosome coherence, %	Total quantity of disturbed mitoses, %
	Fragments	Bridges				
		Without fragments	With fragments			
30 min	22,91±1,23	8,80±0,82	4,18±0,58	35,89±1,40	6,93±0,74	42,82±1,44
5 h	26,60±1,14	16,60±0,96	13,93±1,01	57,13±1,28	4,33±0,52	61,46±1,26
1st day	5,42±0,62	7,25±0,71	1,52±0,35	14,19±0,96	6,49±0,68	20,68±1,12
2 »	1,41±0,35	3,84±0,56	—	5,25±0,64	8,75±0,81	14,00±1,00
5 »	0,60±0,24	2,50±0,49	—	3,10±0,55	9,40±0,92	12,50±1,04
10 »	0,63±0,28	2,62±0,56	—	3,25±0,62	8,12±0,96	11,37±1,12
Control	0,61±0,30	0,61±0,30	0,15±0,15	1,37±0,45	4,54±0,81	5,91±0,92

TABLE 3. DIFFERENCE SIGNIFICANCE (t) IN VARIOUS TYPES OF MITOTIC DISTURBANCES
AMONG GROUPS OF EXPERIMENTAL ANIMALS AND CONTROLS.

Time of sacrifice (time after exposure)	II (100 r) and III (V + 100 r) groups			II (100 r) and IV (100 r + V) groups			III (V + 100 r) and IV (100 r + V) groups			I (V) Group and control		
	Chromosome rearrange-ments	Chromosome coherence	Total of disturbed mitoses	Chromosome rearrange-ments	Chromosome coherence	Total of disturbed mitoses	Chromosome rearrange-ments	Chromosome coherence	Total of disturbed mitoses	Chromosome rearrange-ments	Chromosome coherence	Total of disturbed mitoses
30 min	8,9	-4,4	9,2	0,3	0,4	0,5	10,2	-3,9	5,8	2,4	2,0	2,9
5 h	3,7	-5,2	2,9	3,2	—	3,8	2,1	—	-1,6	0,1	0,3	0,3
1st day	-0,1	-3,2	-2,6	0,03	-0,2	0,1	-0,5	-2,2	-2,0	0,3	7,3	6,6
2 "	5,6	-5,1	0,1	3,2	—	1,4	2,0	0,5	1,5	0,3	1,3	1,3
3 "	2,3	1,9	3,7	—	—	—	—	—	—	1,0	3,2	3,4
5 "	1,5	1,5	2,3	0,4	-0,3	-0,03	1,0	1,7	2,1	0,7	4,1	4,1
10 "	1,2	—	0,5	-0,5	-0,9	0,5	1,3	0,9	-0,1	—	3,5	3,2

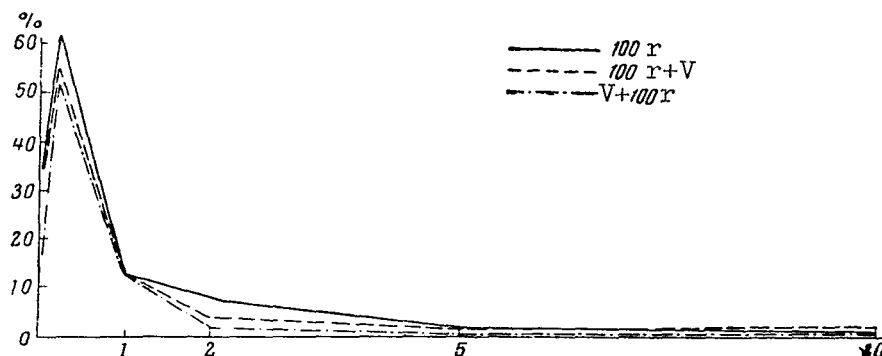


Figure 2. Frequency of chromosome rearrangements (in percent) in the cells of the bone marrow of animals in the second (100 r), third (V + 100 r) and fourth (100 r + V) groups. Abscissa--time in days after exposure.

Comparison of the results in the second (100 r) and third (V + 100 r) groups (table 3) showed that the frequency index of chromosome rearrangements was lower in the third than in the second group (except in the "1st day" ¹⁶⁹ period). The total percentage of disturbed mitoses was also lower in the third group at most periods (30 min, 5 h, 3, 5 and 10 days) than in the second. The decrease of disturbed mitoses occurred basically at the cost of increased frequency of chromosome rearrangements.

In table 3 the indices of the second and third groups are also compared (controls are omitted). We noted a significant decrease in the frequency index of chromosome rearrangements occurring at the 5th hour and 2nd day periods after combined exposure, as compared to the effect of irradiation alone. At other periods there was no substantial difference between these groups in the frequency of chromosome rearrangements. At the 5th hour period we noted a significant decrease ($t = 3.8$; $D < 0.01$) of the total percentage of disturbed mitoses in the fourth group; at other periods the frequency indices of disturbed mitoses differed very little in both groups.

Analysis of the frequency indices of disturbed mitoses in the third (V + 100 r) and fourth (100 r + V) groups (table 3) showed that there were more disarranged chromosome cells in the fourth group than in the third at all periods, except on the first day. The difference was significant at the 30 min period ($t = 3.0$; $D < 0.01$), and most significant at the 5th hour ($t = 2.1$; $0.02 < D < 0.05$) and 2nd day periods ($t = 2.0$; $0.02 < D < 0.05$). The total percentage of disturbed mitoses in the 30 min period of the fourth group reliably exceeded that of the third group ($t = 5.8$; $D < 0.01$). At other periods the frequency index of disturbed mitoses in group 4 fluctuated above and below the level of the third group (there was no significant difference).

Figure 3 represents the average frequency indices of chromosome rearrangements in the cells of the second, third and fourth groups. The percentage was computed in the following manner: the frequency indices of chromosome rearrangements at all periods of the experiment were totaled and the amount

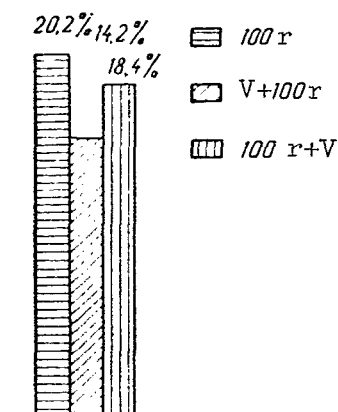


Figure 3. Average frequency of chromosome rearrangements (in percent) in bone marrow cells of animals in second (100 r), third (V + 100 r) and fourth (100 r + V) groups.

obtained divided by the number of periods. Since in the fourth group no analysis was made on the 3rd day after exposure, this period was also neglected in the other groups. The frequency index of chromosome rearrangements in the controls was omitted.

Figure 3 shows that the maximal average frequency of chromosome rearrangements was found in the second group (20.2 percent); it was lower in the fourth (18.4 percent), and lowest in the third group (14.2 percent).

The analysis of disturbed mitoses included, aside from cells with chromosome rearrangements, cells with cohering chromosomes. As shown in table 1, the frequency index of chromosome coherence was altered after vibration as well as after irradiation. The third (V + 100 r) and fourth (100 r + V) groups are, therefore, compared with both the first (V) and the second group (100 r).

Table 3 shows that the frequency index of chromosome coherence in the third group significantly ($D < 0.01$) exceeded that of the second at the first four periods. On the 3rd, 5th and 10th day no significant differences were found between these two groups.

The frequency indices of chromosome coherence in the first and third /170 groups were also compared. At the 30 min and 5th hour periods there were significantly more chromosome coherences in the third group than in the first; at other periods there was no substantial difference between these groups. No significant difference was found in the frequency index of chromosome coherences between the second and the fourth groups (table 3).

Figure 4 gives the average frequency indices of chromosome coherence for all four groups (the computation here and in table 4 is the same as for figure 3). The maximum amount of chromosome coherences was found in the third group (5.1 percent), then in the first (3.0 percent), fourth (2.8 percent) and second (2.2 percent).

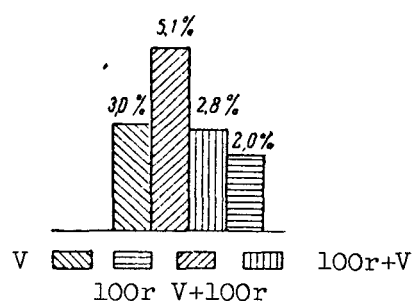


Figure 4. Average frequency of chromosome coherence (in percent) in bone marrow cells of first (V), second (100 r), third (V + 100 r) and fourth (100 r + V) groups of animals.

TABLE 4. ANALYSIS OF AVERAGE RESULTS ON BONE MARROW IN ANIMALS OF VARIOUS GROUPS.

Group	Rearrangements, %			Chromosome coherence, %	Total quantity of disturbed mitoses, %
	Fragments	Bridges	Total		
Group 1 (V)	0.69 ± 0.10	2.02 ± 0.14	2.72 ± 0.17	10.03 ± 0.33	12.75 ± 0.37
Group 2 (100 r)	8.72 ± 0.30	11.54 ± 0.35	20.26 ± 0.42	9.15 ± 0.30	29.41 ± 0.49
Group 3 (V + 100 r)	6.72 ± 0.26	7.92 ± 0.28	14.64 ± 0.36	11.39 ± 0.33	26.03 ± 0.45
Control	0.57 ± 0.17	1.78 ± 0.24	2.33 ± 0.28	6.87 ± 0.47	9.20 ± 0.52

Table 4 represents the analysis of the average data in the first and third groups. The frequency index of chromosome rearrangements in the second group significantly exceeded the one in the third (20.26 ± 0.42 percent and 14.64 ± 0.36 percent; $t > 3$; $D < 0.01$). In the third group there was a decrease in the frequency indices of both fragments and bridges. The difference in the frequency indices of chromosome rearrangement between the first group and the control was not significant. The frequency index of chromosome coherence in the third group notably exceeded those of the first and second groups ($D < 0.01$); the difference between the first and second group was not significant, but was higher in the first group than in the second ($t = 1.95$; $0.05 < D < 0.1$). The total percentage of disturbed mitoses was highest in the second

group; for this index the differences among the three groups were all significant.

The present analysis permits the assumption that combined exposure to irradiation and vibration does not increase the effect of radiation. We even observed a certain decrease in the frequency index of disturbed mitoses after combined exposure (vibration + irradiation). The average frequency indices of chromosome rearrangements were in this order: II (100 r) > IV (100 + V) > III (V + 100 r); and the average frequency indices of chromosome cohesion: III > I > IV > II.

We must remember, however, that cells do not respond with the same sensitivity to the action of agents at diverse stages of the cycle. Amand (1956) has shown in the neuroblasts of the cricket, Sax and Swanson (1914) and N. L. Delone (1958, 1963) in *Tradescantia*, that the prophase is the most sensitive phase to irradiation. Dewey, Humphrey (1962), N. P. Dubinin and L. G. Dubinina (1963) found in tissue cultures a maximal sensitivity to irradiation at the prophase and synthesis (S) stages. Devik (1962) observed an alteration in the epidermal cells of mice in the duration of the presynthetic period (G_1) after

irradiation. It is not excluded that various exposures can diversely alter the duration of the cycle, which could affect the results. We will obtain a more precise answer concerning the nature of the combined effect of irradiation and vibration by analysis of the dynamics of disturbed mitoses for the duration of the cell cycle.

Effect of vibration (70 cps) and irradiation (50 r)

As already mentioned, the facts obtained are insufficient to draw a final conclusion with regard to the combined effect of vibration and irradiation on the cell. It is indispensable to compare the dynamics of cell cycle disturbances after exposure to combined action and irradiation alone. The results of such an analysis are given in this section.

Since a more pronounced effect was observed when vibration preceded ¹⁷² irradiation (V - 100 r) than when it followed it (100 - V), we studied the combined effect in the former sequence (vibration + irradiation).

The 50 r dose was used, since the 100 r dose induces too many chromatic rearrangements, which creates difficulties for the classification of disturbances.

The vibration was vertical, at a frequency of 70 cps, 0.4 mm amplitude and 20 min duration.

The experimental animals were divided into three groups:

- group 1, vibration at 70 cps (V)
- group 2, irradiation at 50 r (50 r)
- group 3, vibration at 70 cps + irradiation at 50 r (V + 50 r).

Altogether 161 animals were examined, of which 18 were biological controls. Over 50,000 cells were analyzed.

Two series of mice were used for the analysis during the first day; the first group, therefore, had its own controls (table 5), whereas the second and third groups had common biological controls (tables 6 and 7).

The animals were sacrificed after 30 min, 1 h, 2 h 30 min, 5, 7, 10, 15, 18, 24, 28, 32, 36, 42 and 48 hours after exposure.

Tables 6 and 7 show the frequency variations of nuclear disturbances in the bone marrow of the second (50 r) and third (V + 50 r) groups.

We can see that up to 2 h 30 min more than 50 percent of all the chromosome rearrangements involved the fragments. After 5 to 7 hours the frequency indices of the bridges and fragments became about equal, then until the 28th to 32nd hour the indices of the bridges exceeded those of the fragments. Beginning after the 32nd hour, the relation of the bridges and fragments evened up again and remained steady to the end of the analysis, i.e., until the 48th hour. The frequency index of chromosome bridges reached its peak after 10 hours (2.67 percent in the second group and 2.28 percent in the third).

TABLE 5. FREQUENCY OF DISTURBANCES IN BONE MARROW CELLS OF MICE AFTER EXPOSURE TO VIBRATION (70 cps). /173

Time of sacrifice (time after exposure)	Fragments	Rearrangements, % Bridges		Total	Chromosome coherence, %	Total quantity of disturbed mitoses, %
		Chroma- tid	Chromo- some			
First day						
30 min	0,57±0,23	0,29±0,16	—	0,86±0,28	3,81±0,59	4,67±0,65
1 h	0,60±0,22	1,12±0,29	0,17±0,12	1,89±0,40	5,09±0,65	6,98±0,75
5 »	0,66±0,27	0,66±0,27	—	1,32±0,37	3,23±0,59	4,55±0,69
10 »	0,37±0,21	0,37±0,21	—	0,74±0,30	4,14±0,69	4,88±0,75
14 »	0,50±0,25	0,25±0,18	—	0,75±0,30	4,50±0,73	5,25±0,79
20 »	0,11±0,11	0,44±0,22	—	0,55±0,24	3,56±0,62	4,11±0,66
24 »	0,29±0,17	0,09±0,09	—	0,38±0,19	5,81±0,82	6,19±0,74
Average value	0,44±0,08	0,48±0,08	0,02±0,02	0,92±0,12	4,31±0,25	5,31±0,28
Control	0,70±0,22	0,42±0,17	—	1,12±0,28	3,42±0,48	4,54±0,57
Second day						
24 h	0,80±0,33	0,26±0,20	—	1,06±0,39	4,14±0,72	5,20±0,81
32 »	0,80±0,33	0,80±0,33	—	1,60±0,46	3,47±0,64	5,07±0,79
42 »	0,80±0,33	0,26±0,20	—	1,06±0,39	4,67±0,77	5,73±0,85
48 »	0,60±0,35	—	—	0,60±0,35	4,40±0,92	5,00±0,97
Average value	0,75±0,16	0,33±0,11	—	1,08±0,20	4,17±0,38	5,25±0,42
Control	0,47±0,17	0,24±0,11	—	0,71±0,20	3,11±0,42	3,82±0,46

TABLE 6. FREQUENCY OF DISTURBANCES IN BONE MARROW OF MICE AFTER IRRADIATION EXPOSURE (50 r) AND COMBINED EXPOSURE (V + 50 r).

Time of sacrifice (time after exposure)	Fragments		Rearrangements, % Bridges Chromatid Chromosome						Total	Chromosome coherence, %				Total quantity of mitotic disturbances, %		
			50 r	V + 50 r	50 r	V + 50 r	50 r	V + 50 r		50 r	V + 50 r	Difference significance (t)	50 r	V + 50 r	Difference significance (t)	50 r
30 min	14,85± ±0,79	11,33± ±0,82	5,85± ±0,52	4,87± ±0,52	0,20± ±0,10	0,53± ±0,17	20,90± ±0,91	16,73± ±0,96	-3,04	4,25± ±0,45	3,74± ±0,49	-0,50	25,15± ±0,97	20,47± ±1,04	-3,27	
1 hh	21,88± ±1,00	23,82± ±1,03	8,17± ±0,66	8,47± ±0,68	0,12± ±0,08	— —	30,17± ±1,11	32,29± ±1,11	1,35	3,06± ±0,41	3,83± ±0,47	1,24	33,23± ±1,14	36,12± ±1,17	1,97	
2 h 30 m.	17,57± ±1,00	17,20± ±0,83	8,26± ±0,73	8,77± ±0,62	0,56± ±0,20	0,19± ±0,10	26,39± ±1,13	26,16± ±0,95	-0,16	3,12± 0,46±	2,65± ±0,35	-0,82	29,51± ±1,20	28,81± ±0,98	-0,45	
5 hh	14,86± ±0,91	12,84± ±0,77	15,07± ±0,92	15,15± ±0,87	1,06± ±0,84	0,83± ±0,22	30,99± ±1,18	28,82± ±1,10	-1,28	±1,64 ±0,33	5,09± ±0,54	5,47	32,63± ±1,20	33,91± ±1,13	0,77	
7 »	10,67± ±0,80	12,81± ±0,83	14,27± ±0,91	15,00± ±0,89	1,86± ±0,35	1,50± ±0,30	26,80± ±1,14	29,31± ±1,14	1,58	2,00± ±0,36	2,06± ±0,36	0,16	28,80± ±1,17	31,37± ±1,16	1,57	
10 »	6,09± ±0,48	7,57± ±0,70	±13,71 ±0,73	16,79± ±0,99	2,67± ±0,36	2,28± ±0,40	22,47± ±0,93	26,64± ±1,18	2,78	2,28± ±0,39	3,86± ±0,51	2,47	24,75± ±0,96	30,50± ±1,23	3,69	
15 »	5,00± ±0,60	5,47± ±0,58	9,69± ±0,82	9,00± ±0,87	0,77± ±0,24	0,40± ±0,16	15,46± ±1,00	14,87± ±0,92	-0,43	2,00± ±0,39	3,46± ±0,47	2,39	17,46± ±1,05	18,33± ±0,99	0,60	
18 »	3,36± ±0,52	3,80± ±0,49	9,34± ±0,83	8,87± ±0,86	1,15± ±0,32	0,40± ±0,16	13,85± ±0,98	13,07± ±0,87	-0,59	3,28± ±0,51	2,33± ±0,39	-1,48	17,13± ±1,08	15,40± ±0,93	-1,22	
24 »	2,57± ±0,40	2,07± ±0,37	6,93± ±0,68	4,50± ±0,56	0,71± ±0,22	0,28± ±0,14	10,21± ±0,81	6,85± ±0,65	-3,26	1,57± ±0,33	4,21± ±0,54	4,19	11,78± ±0,86	11,07± ±0,84	-0,59	
Average value	10,16± ±0,26	10,77± ±0,26	10,15± ±0,26	10,16± ±0,26	1,01± ±0,083	0,71± ±0,07	21,92± ±0,36	21,64± ±0,35	-0,56	2,57± ±0,14	3,47± ±0,15	4,29	24,49± ±0,36	25,11± ±0,36	1,73	
Control	0,45±0,20		0,73±0,26		0,090±0,089		1,27±0,34			4,91±0,34			6,18±0,73			

TABLE 7. FREQUENCY OF DISTURBANCES IN BONE MARROW OF MICE
AFTER IRRADIATION EXPOSURE (50 r) AND COMBINED EXPOSURE
(V+50r).

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Time of sacrifice (time after exposure)	Fragments		Second day										Total quantity of mitotic disturbances, %		
			Rearrangements, % Bridges				Total		Chromosome coherence, %						
	50 r	V + 50 r	Chromatid Chromosome					50 r	Difference significance (t)	50 r	V + 50 r	Difference significance (t)	50 r	V + 50 r	Difference significance (t)
			50 r	V + 50 r	50 r	V + 50 r	50 r								
24	2,78± ±0,56	1,45± ±0,39	4,00± ±0,65	4,11± ±0,66	0,44± ±0,20	0,44± ±0,22	7,22± ±0,86	6,00± ±0,80	-1,04	3,22± ±0,59	4,77± ±0,71	1,68	10,44± ±1,01	10,77± ±1,03	0,30
28 »	1,22± ±0,36	1,66± ±0,41	2,22± ±0,49	2,00± ±0,47	0,33± ±0,17	0,22± ±0,14	3,77± ±0,64	3,83± ±0,65	0,10	3,11± ±0,57	4,33± ±0,68	1,37	6,88± ±0,92	8,21± ±0,92	1,06
32 »	1,25± ±0,41	1,22± ±0,40	1,11± ±0,39	1,76± ±0,48	0,55± ±0,28	—	2,91± ±0,62	2,98± ±0,62	0,09	2,91± ±0,62	3,39± ±0,67	0,52	5,82± ±0,88	6,37± ±0,88	0,46
36 »	1,11± ±0,38	0,80± ±0,33	0,97± ±0,36	0,54± ±0,24	0,28± ±0,20	0,27± ±0,20	2,36± ±0,56	1,61± ±0,46	-1,03	2,08± ±0,54	3,52± ±0,68	1,65	4,43± ±0,78	5,13± ±0,81	0,62
42 »	0,53± ±0,27	0,60± ±0,35	0,53± ±0,27	0,40± ±0,28	—	—	1,07± ±0,36	1,00± ±0,45	-0,09	3,33± ±0,65	4,00± ±0,88	0,59	4,40± ±0,75	5,00± ±0,97	0,48
48 »	0,40± ±0,28	0,40± ±0,28	0,40± ±0,28	0,60± ±0,35	—	—	0,80± ±0,40	1,00± ±0,45	0,33	2,20± ±0,65	3,00± ±0,76	0,80	3,00± ±0,76	4,00± ±0,88	0,86
Average value	1,21± ±0,16	1,02± ±0,15	1,54± ±0,18	1,57± ±0,19	0,27± ±0,077	0,16± ±0,061	3,02± ±0,26	2,75± ±0,26	-0,73	2,81± ±0,26	3,84± ±0,30	2,58	5,83± ±0,35	6,59± ±0,37	1,40
Control	0,47±0,17		0,24±0,11		—		0,71±0,20		3,11±0,42			3,82±0,46			

The maximal quantity of chromosome rearrangement was found in the second group (50 r) at the 1st hour and 5th hour periods (30.17 and 30.99 percent, respectively), and in the third group (V + 50 r) at the 1st and 7th hour (32.29 and 29.31 percent, respectively).

The frequency index of cells showing chromosome coherence in irradiated animals (50 r) presented a slight increase (4.25 percent) after 30 min; it then remains approximately steady, not exceeding the control level.

The frequency index of chromosome coherence in animals exposed to combined action (V + 50 r) remained at the control level during the first day; on the second day it increases. Forty-eight hours after exposure the frequency index of cells with disturbed mitoses hardly exceeded that of the controls.

Comparison of the results between the second and third groups showed that the frequency index of rearrangements in the second group, at the 30 min and 24th hour periods, significantly exceeded that of the third group¹ (table 6).

¹In the series of animals used for the analysis on the second day the difference noted was not significant. However, the variation in both cases was in the same direction, which permits this conclusion.

At the 10th hour period, however, the frequency of rearrangements in the third group most reliably exceeded that of the second ($t = 2.78$; $D < 0.01$).

The frequency index of chromosome cohesion was higher in the third group than in the second at most periods (1, 5, 10, 15 and 24 hours); however, a reliable difference ($t > 3$) was observed only at the 5th hour and 24th hour periods.

The total amount of disturbed mitoses was higher in the second group than in the third 30 min after exposure; 10 hours after exposure the reverse was true.

On the second day after exposure (table 7), the frequency index of rearrangements did not substantially differ in both groups.

In the class of chromosome coherence the differences were also insignificant; however, the variations were unilateral at all times. There were more cases of chromosome coherence in the third group than in the second.

In regard to the frequency index of chromosome bridges no significant differences were found between the two groups; however, there was a tendency toward greater frequency in the second group.

An analysis of the average results has shown (tables 6 and 7) that, in spite of the differing frequency indices at individual time periods, there was no reliable difference between the second and third groups in the total quantities of disturbed mitoses (24.49 percent in the second group and 25.11 percent in the third group on the first day; 5.83 and 6.59 percent, respectively, on the second day). The average frequency indices of the fragments and chromatid bridges also failed to show a significant difference. However, on the first day the average frequency index of chromosome bridges in the second group was considerably higher than in the third group ($t = 2.73$; $D < 0.01$). Also, during the first and second day the average frequency index of chromosome coherence in the third group exceeded the index of the second ($t = 4.29$; $t = 2.58$; $D < 0.01$).

The decreased frequency index of chromosome bridges in the third group ($V + 50$ r) indicates that the presynthetic stage had been affected (Dubinin and Dubinina, 1963).

Moreover, a study was made of the mitoses in bone marrow of the animals after exposure to a frequency of 70 cps (group 1). The results of this ^{/177} analysis are given in table 5. The frequency index of chromosome rearrangements in the bone marrow of this group did not notably differ from the control at any time, although there were fluctuations in both directions of the control index level. In regard to the frequency index of chromosome coherence, two maximums were observed after the 1st and the 24th hour; at other periods (except after the 5th and 20th hour) the frequency index had a tendency to increase after vibration. The increased frequency of chromosome coherence resulted in turn in a general increase of disturbed mitoses at these points. The occurrence of chromosome coherences after vibration exposure indicates that the vibration chiefly affects the late prophase stage (La Cour, Rutishauser, 1954).

Alterations induced by vibration appeared more distinctly when we compared the average results of the first group with those of the control. On the first day the frequency index of chromosome rearrangements was somewhat lower in the first group of animals than in the controls; on the second day, it exceeded that of the controls. However, the lack of dependability of the difference between these groups, together with the "denomination" fluctuations from the level of the control index, indicated that the differences obtained were accidental.

The average frequency index of chromosome cohesion was increased on the first and second day after exposure (table 5), which in turn resulted in a general increase of disturbed mitoses. The unilateral deviation from the control index level confirms our earlier conclusion that vibration increases the frequency index of disturbed mitoses in the bone marrow of mice.

In our study we observed the inhibition of mitotic activity after exposure to irradiation, as did many other authors (Devik, Loothe, 1955; Karpfel, 1961; Knowlton, Widner, 1950). In both group 1 and group 2 the minimum mitotic index occurred 1 hour after irradiation; after 5 hours the mitotic index was restored to the control level. The fluctuations of mitotic activity observed afterwards did not exceed the limits of those in the control (fig. 5).

No alteration of mitotic activity was observed after exposure to vibration (fig. 6).

Thus, the detailed comparative analysis did not reveal an increased frequency index of disturbed mitoses after combined exposure, as compared to the effect of irradiation alone.

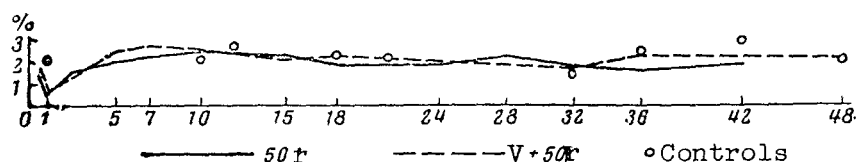


Figure 5. Alterations of mitotic activity (in percent) in bone marrow of mice after irradiation (50 r) and combined exposure (V + 50 r).
Abscissa--time in hours after exposure.

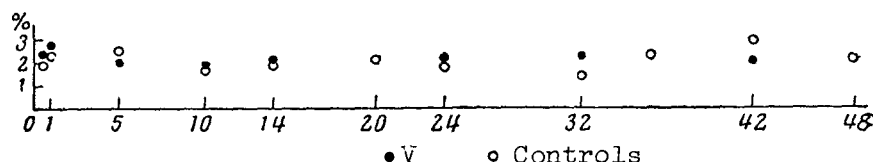


Figure 6. Mitotic activity of bone marrow of mice after exposure to vibration (70 cps).
Abscissa--time in hours after exposure.

We noted a divergence in the frequency indices of certain types of mitotic disturbances. After combined exposure the frequency index of cells presenting chromosome rearrangements decreased somewhat and that of cells presenting chromosome cohesion increased.

We assume that our analysis comprised at least one cytological cycle of the bone marrow, since the frequency index of mitotic disturbances decreased in the experimental groups almost to the level of the controls. According to Zaslomovskaya's latest data (1963), the duration of the cycle in the bone marrow of mice is approximately 14 hours in the erythroids and 21 hours in the myeloids. In the case of our irradiation experiments the cycle was extended. A similar pattern was established earlier in vitro and in vivo in a number of subjects (Chu, Gils, Passano, 1961; Knowlton, Widner, 1950; Dubinin and Dubinina, 1963, and others).

A detailed analysis of the bone marrow in the animals exposed to vibration confirmed our earlier conclusion that vibration increases the frequency index of disturbed mitoses, which is a consequence of an increased frequency of chromosome-cohering cells.

No difference was found in the dynamics of mitotic activity between the combined exposure and irradiation alone; vibratory action does not substantially alter the mitotic activity.

Figure 7 illustrates the results of irradiation exposure at 100 r and 50 r and of combined exposure to vibration (60 cps; 0.44 mm; 20 min) and irradiation at 50 r. The graph shows the common points for both experiments. We note that the curves representing the total quantity of chromosome rearrangements correspond well with each other. The coincidence of the results of both experiments, in which different doses and different vibrations were used, confirms our assumption: the vibration administered before irradiation does not increase the total quantity of destroyed mitoses as compared to irradiation alone. Exposure to vibration alone increases the frequency index of chromosome coherences (fig. 8). Two groups of animals were exposed to vibratory action at a frequency of 70 cps; each of these groups had its own control (table 7). Figure 8 gives the average value of the borderline point between two groups, 24 hours after exposure. The frequency index of chromosome coherence is given separately for each group.

What can be said concerning the mechanism of vibratory action? In experiments by Conger (1948) and Sax (1943), the mechanical factors (sound vibration at a frequency of 9100 cps and centrifugation) altered the effect of irradiation, but did not themselves affect the cells. Our observation was somewhat similar. Exposure to vibration of nonirradiated mice altered only the frequency index of chromosome coherence, which normally was rather high (tables 1, 2, 5, 6 and 7). No alteration in the frequency index of chromosome rearrangements was observed. Vibration combined with irradiation had a modifying effect, since the chromosome rearrangements appeared as a result of irradiation.

Conger and Sax assume that sound vibration and centrifugation affect the process of chromosome separation and reunion mechanically. In our experiments

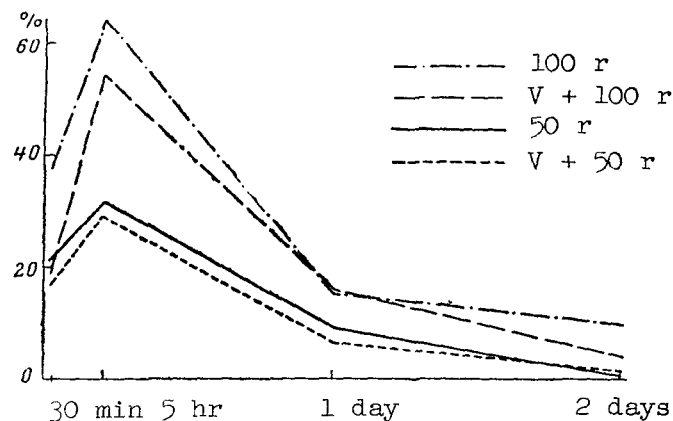


Figure 7. Dynamics of chromosome rearrangement (%) in cerecral cortex cells of mice after irradiating with dosage of 100 r, combined action of irradiation with dosage of 100 r and vibration of 60 cps (V + 100 r), irradiation in 50 r dosage, combined action of irradiation with 50 r dosage and vibration of 70 cps (V + 50 r).

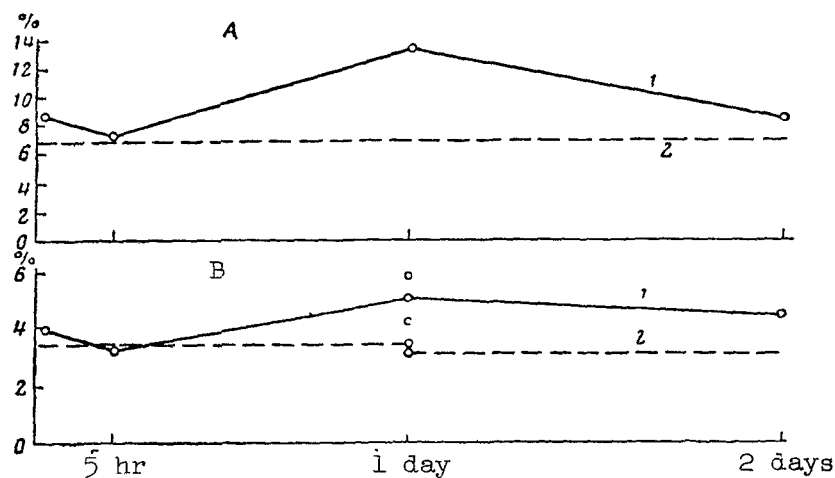


Figure 8. Dynamics of chromosome coherence (in percent) in cells of bone marrow of mice after exposure to vibration at 60 cps (A) and 70 cps (B).

this possibility is not excluded; nevertheless, owing to the low vibration frequency, the mechanical effect should be insignificant. Moreover, there is the possibility of a mediated effect of vibration by the nervous system or the mechanism of biochemical changes in the bone marrow. It has been shown that the effect of vibration alters the serotonin level of the blood (Shashkov,

Antipov et al., 1962) and the pulse rate and the blood pressure (Georgiyevskiy, Yuganov, 1962; Gaerman, 1940). Dilatation and contraction of the blood vessels alter the oxygen metabolism (Andreyeva-Galanina et al., 1961), and there is also a communication concerning the direct effect of vibration on the central nervous system (Ganshina, 1961). The cytological effectiveness of certain metabolites (hormones) has been shown by O. I. Epifanova (1962), N. I. Shapiro et al. (1955). At present, further particulars concerning the vibratory effect on the cell cannot be given.

Conclusion

1. Vibration induces an increase in the frequency index of disturbed mitoses in the bone marrow cells. This increase involves chiefly the frequency index of cells presenting cohering chromosomes.

2. The combined action of vibration and irradiation does not increase the frequency indices of cells having disturbed mitoses above the level of irradiation alone. Nevertheless, the aspect of disturbed mitoses after combined exposure differs from the aspect after irradiation alone: combined action increases the frequency index of cells presenting chromosome coherence and decreases the frequency index of cells with chromosome bridges.

3. The mitotic activity of the bone marrow in irradiated animals (at 50 r) did not differ from the mitotic activity of the bone marrow after combined exposure (V + 50 r).

4. No changes in mitotic activity were found after exposure to vibration (at 70 cps), as compared to the control level.

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Translated for the National Aeronautics and Space Administration
by John F. Holman Co. Inc.